Diuretic Action of Sodium-Glucose Cotransporter 2 Inhibitors and Its Importance in the Management of Heart Failure

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Primarily, the sodium-glucose cotransporter 2 (SGLT2) inhibitors suppress the cotransport of glucose and sodium from the tubular lumen of the proximal tubules to the blood, and excrete glucose into the urine. Therefore, glucose and caloric balances become negative, reducing both the blood glucose level and insulin secretion. On the other hand, the proximal tubular fluid, constituted with low chloride concentration because of SGLT2 inhibition, is transferred to the loop of Henle. Under low chloride conditions, the reabsorption mechanisms in the loop of Henle do not work, similar to when loop diuretics are given. Subanalysis data on heart failure (HF) from the EMPA-REG OUTCOME trials are discussed, assuming that SGLT2 inhibitors are loop diuretics. Renin-angiotensin system inhibitors and β-blockers contribute to prognostic improvements of HF, independent of SGLT2 inhibitors, and therefore, both regimens are essential for the treatment of HF. On the other hand, the prognostic improvements by SGLT2 inhibitors are not significant under treatment including conventional diuretics such as loop diuretics and aldosterone antagonists, suggesting that the prognostic improvement in HF by SGLT2 inhibitors is mostly through their diuretic action. *(Circ J 2016; 80: 2277–2281)*

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Sodium-glucose cotransporter 2 inhibitors (SGLT2-Is), oral antidiabetic agents, are drugs that inhibit glucose reabsorption in the renal proximal tubules and excrete glucose into the urine, resulting in lowered blood glucose. SGLT2-Is are unique antidiabetic agents because they lower blood glucose independently of insulin, and therefore suppress insulin secretion. The large-scale EMPA-REG OUTCOME clinical trials revealed for the first time that SGLT2-Is show prognostic improvements on the heart and kidneys as hypoglycemic drugs. In this review, the focus will mainly be on the mechanisms of how SGLT2-Is and their combinations with other diuretics improve the prognosis of heart failure (HF).

**Loop Diuretic Action of SGLT2 Inhibitors**

In the kidneys, not only waste products (unnecessary matter) but also essential nutrients (necessary matter) such as glucose and amino acids are filtered through the glomeruli in a non-selective manner. Then, in the proximal tubules, connected to the glomeruli, only essential nutrients are transported selectively from the glomerular filtrate to the blood based on active transport using energy. This transport process is referred to as tubular reabsorption. In healthy subjects, neither glucose nor amino acids are detected in the urine because of their complete reabsorption in the proximal tubules.

SGLT2-Is suppress the cotransport of glucose coupled with sodium (Na) from the lumen of the proximal tubules into blood. The proximal tubules have multiple options to reabsorb Na, in addition to SGLT2. Therefore, Na reabsorption proceeds even in the presence of SGLT2-Is. Because the proximal tubules are highly permeable, water is reabsorbed to keep the tubular fluid isotonic to blood. As a result, the ratio of Na as well as chloride (Cl) to water, which is 4:8 at the proximal tubular origin (=glomerular filtrate), gradually changes to 3:7 and further to 2:6 as shown in Figure 1. Because glucose reabsorption depends on SGLT2, on the other hand, glucose acts as a non-reabsorbable substance under SGLT2-Is administration. Therefore, the absolute amount of glucose is maintained at 4 and does not decrease. In this way, the total solute concentration in the proximal tubules remains constant and isotonic as 8/8, 7/7, and 6/6. It should be noted here, however, that the concentrations of both Na and Cl significantly decrease gradually. This low Cl concentration fluid is delivered to the loop of Henle in the next step (Figure 2).

When proximal tubular reabsorption is inhibited, reabsorption in the loop of Henle, located after the proximal tubules, is usually enhanced in a compensatory manner. This is the reason why none of the current diuretic agents inhibit proximal tubular reabsorption. It should be noted, however, that the intraluminal Cl concentration is a rate-limiting step for reabsorption in the loop of Henle. Therefore, a reduction in Cl concentration inhibits reabsorption in the loop of Henle.
whereas the Na or potassium (K) concentration has no influence. A decrease in Cl concentration, as discussed before, results in a significant inhibition of reabsorption in the loop of Henle, probably because the number of necessary Cl molecules is twice the number of Na and K molecules. The reabsorption mechanism in the loop of Henle comprises Na-K-2Cl cotransporters, suggesting that Cl plays an essential role compared with other electrolytes.

In this way, SGLT2-Is primarily act on the proximal tubules, causing osmotic diuresis; however, the effect of osmotic diuresis on tubular reabsorption is quantitatively small. Thus, the inhibition of tubular reabsorption is essentially based on the diuretic action in the loop of Henle rather than that in the proximal tubules. That is, the diuretic action induced by SGLT2-Is is mainly based on secondary inhibition in the loop of Henle. Therefore, it may be reasonably understood that SGLT2-Is act as loop diuretics.

As discussed, SGLT2-Is act as loop diuretics to reduce body fluid volume and have antihypertensive actions comparable to low-dose thiazide diuretics. At the end of the loop of Henle, the macula densa are located, serving as sensors of fluid composition. SGLT2-Is administration causes inhibition of Na reabsorption in the loop of Henle and stimulation of renin secretion via the macula densa, resulting in a reaction similar to that observed with administration of loop diuretics. In fact, there is a report on similar findings that activation of the renin-angiotensin system (RAS) in cases of genetic renal glucosuria due to SGLT2 deficiency.

Prognostic Improvements by SGLT2 Inhibitors in HF

The EMPA-REG OUTCOME trial, including 7,020 type 2 diabetic patients with high cardiovascular risk, reported that cardiovascular and total deaths, as well as hospitalization for HF, were significantly reduced in the SGLT2-Is treatment group compared with placebo (standard treatment) group (P<0.001) during follow-up for 3.1 years. There was a ten-
HF and SGLT2 Inhibitors

**Cardiovascular Prevention and Diuretics**

It has been believed that prevention of the new development of diabetes mellitus is essential to suppress cardiovascular events during antihypertensive therapy, especially with diuretics. SGLT2-Is are primarily antidiabetic drugs that are used to lower blood glucose in patients diagnosed as diabetic. Therefore, SGLT2-Is are expected to have a favorable effect on preventing cardiovascular events through improvements in blood glucose levels. It is also well known that diuretic therapy has remarkable effects on preventing HF and stroke, compared with other antihypertensive therapy. However, it should be considered that the induction of hypokalemia results in the loss of this preventive effect.

SGLT2-Is do not cause hypokalemia, although they have loop diuretic and RAS activation actions. Unlike conventional diuretics, SGLT2-Is reduce serum uric acid. In addition, SGLT2-Is reduce, but do not increase, the heart rate. The precise mechanisms of these unique features as diuretics must be further clarified; however, unlike conventional diuretics, SGLT2-Is are expected to be almost perfect and ideal diuretics.

Because SGLT2-Is have a loop diuretic action, the co-administration of other diuretics may induce dehydration and/or hypotension as will be discussed later. In addition, when RAS inhibitors are used to protect the kidney and other organs, they should be started at a low dose. When SGLT2-Is are administered, RAS is activated and prevents the blood pressure reduction by the diuretic action of the SGLT2-Is. In particular, caution should be exercised when RAS inhibitors are first administered, because blood pressure tends to be dramatically reduced. In the EMPA-REG trial, RAS inhibitors were used in combination with SGLT2-Is in more than 80% of cases, and the cardiovascular/renal protection was confirmed. The long-term benefits of this combination are considered to be significant.

**Why Did SGLT2 Inhibitors Cause Stroke?**

The EMPA-REG OUTCOME trials reported that stroke tended to increase in the SGLT2-Is treatment group (P=0.2). Conventionally to date, diuretics have prevented stroke, as

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**Figure 3.** Hospitalization for heart failure and SGLT2 inhibitors. Subanalysis of the EMPA-REG OUTCOME clinical trials. Different roles of basic regimens (RAS inhibitors and β-blockers) and diuretics (modified with permission by Kimura). RAS, renin-angiotensin system; SGLT2, sodium-glucose cotransporter 2.
SGLT2-Is, which are expected to have a loop diuretic action, increased stroke incidence. A recent meta-analysis reported that SGLT2-Is significantly increased stroke (Figure 4). In the EMPA-REG OUTCOME trials, 43.7% of the SGLT2-Is group (2,047 of 4,687 cases) were treated in combination with diuretics. Details of the types and doses of diuretics administered were unclear. However, given that SGLT2-Is have a loop diuretic action, there is a risk with their combined use with conventional diuretics in about 50% of patients. Combined use of different types of diuretics might result in massive diuresis.

If loop diuretics (SGLT2-Is) are administered alone, Na reabsorption in the distal tubules (action site of thiazides), located after the loop of Henle, is enhanced in a compensatory manner. Therefore, actual diuresis is limited. However, SGLT2-Is use in combination with thiazides may cause massive diuresis. Compensatory Na reabsorption by the distal tubules but also reabsorption in the collecting duct (action site of aldosterone antagonist) are both inhibited, resulting in further massive diuresis. The EMPA-REG data should be re-analyzed regarding whether such combinations were related to stroke (cerebral infarction) or not. Please pay the attention to Figure 3 which shows that the combination of SGLT2-Is and aldosterone antagonists caused worsening of HF, probably through dehydration and low output failure.

There is a report on body fluid volume contraction, such as orthostatic hypotension and syncope, associated with SGLT2-Is administration, especially in elderly patients, although it was not significant. Combined use with conventional diuretics must be applied carefully in regard to volume depletion.

Conclusions

SGLT2-Is function not only as antidiabetics drugs for normalizing blood glucose, but also have diuretic and hypotensive actions to resolve salt-sensitive hypertension, which plays an important role in diabetes. Therefore, SGLT2-Is strongly prevent heart and renal failure. However, data also suggest that SGLT2-Is tend to increase stroke incidence, which instead could be efficiently inhibited by conventional diuretics. It should be studied further why stroke cannot be prevented by SGLT2-Is. It may be possible that conventional diuretics were prescribed in combination with SGLT2-Is in the particular studies, resulting in dehydration and hypotension that lead to cerebral infarction. Because SGLT2-Is are expected to prevent organ damage, such as to the heart and kidneys, further studies, including re-analysis of the EMPA-REG outcome data, are urgently required.

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References


