

Natriuretic effect of SGLT2 and its mechanisms in patients with HF and T2DM

Kaoru Dohi, MD, PhD

Mie University Hospital

Recent randomized multicenter clinical trials have shown that sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce the risk for heart failure (HF) hospitalization in patients with chronic HF and type 2 diabetes (T2DM). These beneficial effects are partly explained by the natriuretic effects of SGLT2 inhibitors.

SGLT2 inhibitors block glucose and sodium reabsorption in the proximal tubule that leads to increased sodium-chloride delivery to the macula densa, and this physiology can explain the smaller neurohormonal response to SGLT2 inhibitors compared to other diuretics including loop diuretics. Indeed, we have reported that the addition of ivermectin to conventional loop or thiazide diuretics for 4 days decreased plasma natriuretic peptide levels without influencing plasma angiotensin II, aldosterone, or noradrenaline levels in a pilot study involving 20 Japanese patients with T2DM and HF. In addition, we have recently demonstrated that combination of lower urine sodium concentration and higher dosage of loop diuretics at baseline strongly predicted the diuretic effects of SGLT2 inhibitors in these patients. These results may suggest that SGLT2 inhibitors restore the responsiveness to loop diuretics in symptomatic HF patients with T2DM. Another study in the United States demonstrated that empagliflozin therapy increased natriuresis as monotherapy and had clinically meaningful synergistic effect when combined with a loop diuretic. These favorable diuretic profiles of SGLT2 inhibitors may offer significant advantage in the management of volume status in HF patients and may be a contributory mechanism to the superior long-term HF outcomes observed with these agents.

Very recent studies have shown that SGLT2 inhibitors reduced the risk of a composite of worsening HF or cardiovascular death among patients with HF and a reduced ejection fraction regardless of the presence or absence of T2DM.

In this talk, I will summarize the key pharmacodynamic effects of SGLT2 inhibitors and the clinical evidence that support the rationale for the use of SGLT2 inhibitors in patients with HF who have T2DM and non-T2DM.