中文題目：不同種類利尿劑在有使用 SGLT2i 或是 DPP4i 糖尿病患者的使用

英文題目：Diuretics in Type 2 Diabetes mellitus patients following SGLT2i or DPP4i treatment

作　　者：劉尚霖，詹益欣，趙子凡，陳紹緯，高亦偉，黃千盈，褚柏顯

服務單位：長庚醫院內科部

Aims:

Sodium–glucose cotransporter 2 inhibitors (SGLT2is) reduce the risks of major adverse cardiovascular events (MACEs), hospitalization for heart failure (HF), and composite kidney outcomes in patients with type 2 diabetes with or without cardiovascular disease. Thiazides (or thiazide-like), loop diuretics, and potassium-sparing agents or mineralocorticoid receptor antagonists (MRAs) are the three main classes of diuretics commonly prescribed to patients with type 2 diabetes for several purposes. Whether diuretics modify the beneficial effect of sodium–glucose cotransporter-2 inhibitors (SGLT2is) on clinical outcomes in patients with type 2 diabetes remains unclear.

Methods:

We used medical data from a multicenter health-care provider in Taiwan and enrolled 11,091 and 7772 patients with diabetes without preexisting heart failure (HF) receiving SGLT2i and dipeptidyl peptidase-4 inhibitor (DPP4i) from June 1, 2016, to December 31, 2018. Patients receiving SGLT2is or DPP4i were categorized based on the use of background diuretics. Patients were followed up from the drug-index date until the occurrence of adverse clinical events, drug discontinuation, or the end of the study period, whichever occurred first.

Results: A total of 22.9% and 20.9% of patients receiving SGLT2i and DPP4i treatment, respectively, were prescribed any diuretic. The use of any of three classes of diuretics, namely thiazide, loop diuretics, and mineralocorticoid receptor antagonists (MRAs), was associated with a steeper slope in initial eGFR decline (all $P<0.001$) but a comparable eGFR slope (all $P>0.05$) after 24 weeks compared with no use of diuretics. The use of the three classes of diuretics was independently associated with a higher risk of a marked initial renal function decline following SGLT2i treatment. Compared with the patients not receiving diuretics, those receiving diuretics had a comparable risk of major adverse cardiovascular events or hospitalization for HF but a higher risk of composite renal outcomes following SGLT2i initiation; this increased risk resulted from the use of loop diuretics and MRAs at baseline after multivariate adjustment. Similarly, the patients receiving loop diuretics or MRAs at baseline had higher risks of hospitalization for HF (only for loop diuretics) and composite renal outcomes following DPP4i initiation. Use of thiazide was not associated with poor clinical outcomes following SGLT2i initiation after multivariate adjustment. The treatment benefit in terms of the reduction of risk of hospitalization for HF and renal outcomes for SGLT2i versus the DPP4i was persistent across the different classes of diuretics (P for interaction >0.05). The use of a diuretic was associated with higher risks of serum potassium imbalance and hyperuricemia following either SGLT2i or DPP4i treatment. However, SGLT2i use was associated with lower risks of serum potassium imbalance and hyperuricemia compared with DPP4i use after multivariate adjustment, and this finding remained persistent across the different classes of diuretics.

Conclusion:

The participants with type 2 diabetes without preexisting HF but treated with diuretics, specifically loop diuretics and MRAs but not thiazide, had worse HF and composite renal outcomes either following SGLT2i or DPP4i treatment. The beneficial effect of SGLT2is relative to that of the DPP4i on cardiovascular and renal outcomes was maintained irrespective of the use of the different classes of diuretics. However, the use of the three classes of diuretics was independently associated with a risk of a marked initial renal function decline following SGLT2i initiation. Therefore, physicians should be vigilant for the early adverse effect of the combination regimen of a diuretic plus an SGLT2i on renal function.