Combined effect of sodium-glucose cotransporter 2 and dipeptidyl peptidase-4 inhibitors for diabetic kidney disease.

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COMMENTARY

Combined effect of sodium–glucose cotransporter 2 and dipeptidyl peptidase-4 inhibitors for diabetic kidney disease

The aim of diabetes treatment is to maintain quality of life and to extend healthy longevity to the same extent as those for healthy people. To achieve this aim, it is important to prevent the progression of diabetic vascular complications. In particular, diabetic kidney disease (DKD) – mainly in individuals with type 2 diabetes – is a leading cause of end-stage renal disease worldwide. Among patients with type 2 diabetes, the progression of DKD markedly increases the risk for other vascular complications, resulting in increased medical care costs related to diabetes treatment. Thus, appropriate management of DKD is clinically and societally relevant in improving prognosis.

DKD is characterized by an increase in albuminuria and a decrease in the glomerular filtration rate (GFR). Increases in albuminuria lead to a higher risk for progression to end-stage renal disease, whereas a reduction in albuminuria is associated with slower deterioration in kidney function accompanied by reduced risk for the onset of macrovascular complications and mortality. Thus, treatment aimed at reducing albuminuria is an important component of therapeutic strategies aimed at improving prognosis in patients with DKD. Presently, comprehensive risk management addressing lifestyle habits and risk factors, including hyperglycemia, hypertension and dyslipidemia, is emphasized with regard to preventing the onset and the progression of DKD[1]. However, strict pharmacological treatment for these risk factors might increase the incidence of adverse effects, such as severe hypoglycemia.

In particular, special considerations for the selection of glucose-lowering medication(s) in patients with DKD are required, owing to an increased risk for adverse effects as a result of reduced kidney function (Table 1). Glucose-lowering drugs, which are cleared by the kidney, require renal dosing adjustment in patients with an estimated GFR (eGFR) <60 mL/min/1.73 m^2. While administering these drugs, kidney function should be carefully monitored, and the efficacy and risk of continuing treatment must be continually reviewed. Furthermore, most of these drugs are contraindicated in those with severely impaired kidney function, such as those with an eGFR <30 mL/min/1.73 m^2. For example, metformin, which is the recommended initial medication for lowering glucose levels in patients with type 2 diabetes, is contraindicated in those with an eGFR <30 mL/min/1.73 m^2, owing to an increased risk for lactic acidosis[2].

Among glucose-lowering medications, some are reported to exert a direct renoprotective effect. Recent large randomized controlled trials reported that sodium–glucose cotransporter 2 (SGLT2) inhibitors are effective for reducing the risk for all-cause mortality and cardiovascular morbidity, and maintaining kidney function in individuals with type 2 diabetes and preserved kidney function[3]. The principle pharmacological action of SGLT2 inhibitors is to inhibit the reabsorption of glucose and sodium at the proximal tubules of the kidney, resulting in lower blood glucose levels and reduced bodyweight. In addition to their glucose-lowering effect, SGLT2 inhibitors are reported to exert numerous osmotic and natriuretic effects, such as decreased systemic blood pressure, intraglomerular pressure, albuminuria and uric acid levels, and increased hematocrit, among others. These multifactorial metabolic and hemodynamic actions most likely cooperatively contribute to renal protection. However, the glucose-lowering effect of SGLT2 inhibitors is attenuated according to worsening kidney function, whereas other renoprotective effects appear to be independent of kidney function[4]. Thus, exploring which glucose-lowering medication(s) should be added if appropriate glycemic control is not

Table 1 | Disadvantages of oral antihyperglycemic agents in patients with type 2 diabetes and reduced kidney function

Class	Disadvantage with reduced kidney function
Biguanides	Increased risk for lactic acidosis
Sulfonylureas	Increased risk for severe hypoglycemia
Meglinitides	Hypoglycemia
α-Glucosidase inhibitors	Gastrointestinal problems including abdominal discomfort, diarrhea and flatulence
Thiazolidinediones	Increased risk for fluid retention and edema
DPP-4 inhibitors	Relatively safe; however, some are required renal dosing adjustment
SGLT2 inhibitors	Attenuated glucose-lowering effect

DPP-4, dipeptidyl peptidase-4; SGLT2, sodium–glucose cotransporter 2.

*Corresponding author. Shin-ichi Araki
Tel.: +81-77-548-2222
Fax: +81-77-543-3858
E-mail address: araki@belle.shiga-med.ac.jp
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achieved in individuals with type 2 diabetes and reduced kidney function treated with SGLT2 inhibitors is an important clinical issue.

Dipeptidyl peptidase-4 (DPP-4) inhibitors are also novel glucose-lowering agents. The pharmacological action of DPP-4 inhibitors is to inhibit the breakdown of glucagon-like peptide-1, which is different from the glucose-lowering mechanism of SGLT2 inhibitors. In clinical practice, DPP-4 inhibitors are widely used, because they confer a low risk for hypoglycemia unless they are administered with drugs that are associated with hypoglycemia, such as insulin and sulphonylureas. Furthermore, the advantage of DPP-4 inhibitors is that they can be used relatively safely and effectively for lowering glucose levels in patients with reduced kidney function, even in those undergoing maintenance hemodialysis, although some DPP-4 inhibitors need dose adjustment as kidney function declines. Additionally, some DPP-4 inhibitors have been reported to reduce albuminuria in some clinical trials. With increasing evidence supporting a role of SGLT2 and DPP-4 inhibitors in type 2 diabetes, combination therapies of these drugs are now available in clinical practice, and have been shown to act in a complementary, synergistic manner to reduce glycated hemoglobin A1c (HbA1c) levels more than that achieved with either agent as monotherapy. However, it remains unclear whether this combination therapy is renoprotective in patients with type 2 diabetes and DKD, as well as its glucose-lowering effects.

The albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin, and the effect of dapagliflozin and saxagliptin on glycemic control in patients with type 2 diabetes and chronic kidney disease (DELIGHT) trial, published in *Lancet Diabetes Endocrinology*, was the first prospective clinical trial to evaluate the efficacy and safety of combination therapy of an SGLT2 inhibitor (dapagliflozin) and DPP-4 inhibitor (saxagliptin) in regard to a reduction in albuminuria and HbA1c in patients with type 2 diabetes and established DKD[5]. This trial was a randomized, double-blind, placebo-controlled clinical study including 448 patients with type 2 diabetes, urine albumin-to-creatinine ratio (UACR) 30–3,500 mg/g Cr and eGFR of 20–80 mL/min/1.73 m^2 who were undergoing stable glucose-lowering and antihypertensive treatments, including renin–angiotensin system blockers. Participants were randomly assigned to receive a placebo, dapagliflozin alone or combination therapy of dapagliflozin and saxagliptin, and followed for 24 weeks. The primary end-point for the dapagliflozin monotherapy group was the percentage change in UACR at 24 weeks and, for the combination therapy group, the percentage change in UACR and HbA1c at week 24 versus baseline. Compared with the placebo, dapagliflozin monotherapy and combination therapy of dapagliflozin and saxagliptin significantly reduced UACR by 21% and 38%, respectively, after 24 weeks of treatment. A reduction of HbA1c in the combination therapy group was also observed throughout the intervention period, and the difference versus the placebo at week 24 was −0.58% ($P < 0.0001$). Additionally, the difference in changes in UACR was consistent, without regard to the responses of HbA1c, bodyweight or blood pressure responses. Importantly, combination therapy with dapagliflozin and saxagliptin was well tolerated by patients with severe kidney dysfunction.

The results of the DELIGHT trial showed that combination therapy with SGLT2 and DPP-4 inhibitors is an attractive therapeutic option to concomitantly and effectively achieve the dual objectives of glucose lowering and albuminuria reduction in patients with DKD, although this trial had some limitations, including a short trial period and small sample size. Similar to previous reports, an initial decrease in eGFR was observed, both with dapagliflozin monotherapy and combination therapy with dapagliflozin and saxagliptin, which was completely reversible after treatment discontinuation. However, this trial could not provide information as to whether the combination therapy delayed progression to end-stage renal disease because of the short trial period. Furthermore, it remains unclear as to whether combination therapy with SGLT2 and DPP-4 inhibitors is effective and safe in patients with more severe kidney dysfunction (eGFR <20 mL/min/1.73 m^2), and those with normoalbuminuric DKD who might have the condition due to cause(s) other than diabetes per se. The mechanism by which this combination therapy more effectively reduces albuminuria in patients with type 2 diabetes and DKD remains to be fully elucidated.

At the same time, the Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study was published[6]. The CREDENCE study showed that canagliflozin (an SGLT2 inhibitor) is effective for risk reduction of renal composite outcome in type 2 diabetes patients with UACR >300 mg/g and an eGFR of 30–90 mL/min/1.73 m^2. Unfortunately, the CREDENCE study did not report data regarding renoprotective effect(s) and safety of concomitant antihyperglycemic treatments, although patients taking DPP-4 inhibitors (approximately 17%) were included at baseline. Thus, in the CREDENCE study, it remains unclear which glucose-lowering drug combined with SGLT2 inhibitors was more effective and safer in patients with DKD. At the minimum, these two trials – DELIGHT and CREDENCE – confirmed and extended previous findings that SGLT2 inhibitors exert a renoprotective effect in patients with type 2 diabetes and moderate-to-severe kidney dysfunction.

There is little doubt that the development of novel therapeutic options for individuals with type 2 diabetes and DKD has made it possible to provide high-quality diabetes care to those with DKD. However, it remains difficult to achieve appropriate comprehensive risk management safely and to maintain kidney function in those with DKD. According to the progression of DKD, the use of many glucose-lowering drugs is restricted, which makes it increasingly difficult to achieve appropriate glycemic

control safely. Thus, it is clinically important to explore therapeutic options that can help individuals with type 2 diabetes and DKD achieve better health outcomes.

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Shin-ichi Araki*
Division of Diabetology, Endocrinology and Nephrology, Department of Medicine, Shiga University of Medical Science, Otsu, Shiga, Japan

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