

CREDESCENCE: A silver lining in the dark cloud of diabetic nephropathy

The management of diabetic nephropathy is one of the major clinical and societal issues because of its widespread prevalence, and massive health and financial burden. In patients with advanced diabetic nephropathy, who have a poor prognosis in terms of kidney function and a high risk of atherosclerotic cardiovascular disease, the only established therapy to reduce the risk of the progression of end-stage kidney disease (ESKD) is pharmacological blockade of the renin-angiotensin system, so far.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have been receiving a great deal of attention owing to their protective effects on the kidney and atherosclerotic cardiovascular disease, recently shown in three large-scale randomized controlled trials^{1–3}. Notably, SGLT2 inhibitors reduced the risk of composite kidney outcomes consisting of a 40% decrease in estimated glomerular filtration rate (eGFR), a doubling of serum creatinine levels and a lower incidence of ESKD, as shown in Table 1. These results were different from those of randomized controlled trials using glucagon-like peptide 1 receptor agonists⁴, which are another class of drugs noted for cardiovascular- and kidney-protective effects. Glucagon-like peptide 1 receptor agonists reduced the risk of progression to macroalbuminuria, but not severe kidney outcomes in large-scale randomized controlled trials, suggesting that the kidney-protective effects of glucagon-like peptide 1 receptor agonists are limited to patients with early-stage diabetic nephropathy. Post-hoc analysis of the Canagliflozin Cardiovascular Assessment

Study program showed that the beneficial effects of the SGLT2 inhibitor, canagliflozin, on kidneys were mostly consistent across patients with varying types of kidney damage^{5,6}. Consequently, the three aforementioned large-scale trials of SGLT2 inhibitors provided desirable results regarding the association of the drugs with kidney end-points in patients with type 2 diabetes. However, the study populations largely consisted of patients with no or mild diabetic nephropathy at baseline, and the kidney-related events were assessed as secondary and exploratory outcomes^{1–3}.

The Canagliflozin and Renal End-points in Diabetes with Established Nephropathy Clinical Evaluation (CREDESCENCE) study⁷ was a randomized, double-blind, placebo-controlled, multicenter clinical trial of 4,401 patients with type 2 diabetes, and was carried out to primarily assess the effects of canagliflozin on kidney disease progression (Table 1). All the patients assessed had a urinary albumin-to-creatinine ratio of >300 to 5,000 mg/g and eGFR of 30 to <90 mL/min/1.73 m², and were treated with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. The primary end-point was a composite of ESKD (kidney replacement therapy or a sustained eGFR of <15 mL/min/1.73 m²), doubling of serum creatinine levels and death due to kidney or cardiovascular disease. The trial was stopped early after a planned interim analysis according to the recommendation of the data and safety monitoring committee, with a median follow-up period of 2.62 years. A 30% risk reduction of the primary end-point was shown in the canagliflozin group (hazard ratio 0.70, 95% confidence interval [CI] 0.59–0.82; $P < 0.001$). Findings with respect to the kidney-specific composite outcome

(ESKD, doubling of creatinine or death from kidney disease) were encouraging (hazard ratio 0.66, 95% CI 0.53–0.81; $P < 0.001$). The number needed to treat calculated by the authors using the Stang's method⁸ was 77 (Table 1). Furthermore, patients treated with canagliflozin had a lower risk for several cardiovascular outcomes. Based on the findings from the CREDESCENCE study, the recommendation from the American Diabetes Association was edited as follows⁹: "Consider use of a sodium-glucose cotransporter 2 inhibitor in patients with an eGFR ≥ 30 mL/min/1.73 m² and particularly in those with >300 mg/g albuminuria to reduce the risk of chronic kidney disease progression, cardiovascular events, or both."

The CREDESCENCE study evidently showed the kidney-protective effects of canagliflozin in patients with advanced diabetic nephropathy. It is necessary to consider the mechanisms underlying the beneficial effects of SGLT2 inhibitors. First, the improvement of blood glucose control, bodyweight and blood pressure owing to canagliflozin might partly contribute to the results, although the between-group mean differences in the three parameters were modest: 0.25% (95% CI 0.20–0.31%), 0.80 kg (95% CI 0.69–0.92 kg) and 3.3 mmHg (95% CI 2.7–3.9 mmHg) in glycated hemoglobin level, bodyweight and systolic blood pressure, respectively. Second, SGLT2 inhibitors suppressed reabsorption of glucose and sodium, restored tubuloglomerular feedback, and reversed glomerular hyperfiltration¹⁰; this might explain the positive findings in the CREDESCENCE study. During the first 3 weeks, there was a greater reduction in eGFR in the canagliflozin group than in the placebo group (-3.72 ± 0.25 vs -0.55 ± 0.25 mL/min/1.73 m²). Thereafter, the eGFR decline

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Table 1 | Summary of the results of four large-scale randomized controlled trials regarding the effects of sodium–glucose cotransporter 2 inhibitors on kidney outcomes

	EMPA-REG OUTCOME trial (n = 7,020)	CANVAS program (n = 10,142)	DECLARE-TIMI 58 study (n = 17,160)	CREDESCENCE study (n = 4,401)
Intervention	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin
Data at baseline				
Age (years)	63	63	64	63
Men (%)	72	64	63	66
History of ASCVD (%)	99	72	41	50
RAAS inhibitors (%)	81	80	81	100
HbA1c (%)	8.1	8.2	8.3	8.3
eGFR (mL/min/1.73 m ²)	74.1	76.5	85.3	56.2
Urinary ACR (mg/g)	NA	12.4 [†]	NA	927.0 [†]
Urinary ACR (mg/g) category (%)				
<30	60	70	69	0
30–300	29	22	24	0
≥300	11	8	7	100
Primary outcome	3-point MACE	3-point MACE	3-point MACE	Composite kidney outcome and cardiovascular death
Composite kidney outcome [‡]				
Hazard ratio (95% CI)	0.54 (0.40–0.75)	0.60 (0.47–0.77)	0.53 (0.43–0.66)	0.66 (0.53–0.81)
Incidence/ 1,000 patient-years				
Intervention group	6.3	5.5	3.7	27.0
Placebo group	11.5	9.0	7.0	40.4
NNT [§]	194	288	305	77

Date is expressed as mean, median, or percentage. ACR, albumin-to-creatinine ratio; ASCVD, atherosclerotic cardiovascular disease; CANVAS, Canagliflozin Cardiovascular Assessment Study; CI, confidence interval; CREDESCENCE, Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis In Myocardial Infarction 58; eGFR, estimated glomerular filtration rate; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in the Type 2 Diabetes Mellitus Patients–Removing Excess Glucose; MACE, major adverse cardiovascular events; NA, not applicable; NNT, number needed to treat; RAAS, renin–angiotensin–aldosterone system; SGLT2, sodium–glucose cotransporter 2. [†]Expressed as the median. [‡]Means a composite of end-stage kidney disease (kidney replacement therapy and/or estimated glomerular filtration rate [eGFR] of <15 mL/min/1.73 m²), kidney insufficiency (40% decline in eGFR or doubling of serum creatinine levels) and kidney-related death. [§]Estimated by the authors using Stang's method.

was slower in the canagliflozin group than in the placebo group. Third, SGLT2 inhibitors have a strong effect in reducing the risk of deteriorating heart failure, which is closely associated with advanced diabetic nephropathy. A recent study of patients with heart failure and a reduced ejection fraction showed that the risk of deteriorating heart failure or death from cardiovascular causes was lower in the dapagliflozin group than in the placebo group, regardless of the presence of diabetes¹¹. Therefore, the kidney-protective effects observed in the CREDESCENCE study might have been noted because of the interruption of the vicious circle involving diabetic nephropathy and heart failure¹².

There are several concerns that need to be resolved before SGLT2 inhibitors

can be used in the therapy for advanced diabetic nephropathy. First, it remains unknown whether the beneficial effects on kidneys shown in the CREDESCENCE study would be confirmed in patients with eGFR of <30 mL/min/1.73 m² and/or urine albumin-to-creatinine ratio of <300 mg/g. Second, it is necessary to clarify whether SGLT2 inhibitors have beneficial effects on kidneys under the absence of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers use in the background. Finally, it is necessary to consider the increased risk of amputation and fracture with canagliflozin that was reported in the Canagliflozin Cardiovascular Assessment Study program¹³. Although the population in the CREDESCENCE study had a

higher risk for both events than that in the Canagliflozin Cardiovascular Assessment Study program, the canagliflozin group in the CREDESCENCE study did not have a higher risk for both events than the placebo group. However, it seems appropriate to avoid use of SGLT2 inhibitors in patients with severe peripheral vascular disease, as it remains unknown whether the difference was because of differences in the populations or protocols to capture these adverse events.

In conclusion, the CREDESCENCE study has provided evidence that canagliflozin administration is a beneficial therapy that delays kidney disease progression in patients with advanced diabetic nephropathy. Further investigations are required to examine the beneficial effects



of SGLT2 inhibitors on kidneys in patients with diabetes and more severe kidney insufficiency and those without diabetes. The CREDENCE study is nothing more than a preface in overcoming diabetic nephropathy.

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DISCLOSURE

The authors declare no conflict of interest.

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