DOI：10.6314/JIMT.202110_32(5).03 內科學誌 2021：32：322-332

The Clinical Landscape of Managing Type 2 Diabetes Patients with Chronic Kidney Disease with Sodium-Glucose Cotransporter-2 Inhibitors: Where are We Now and What can We Expect?

Kuo-Bin Tseng

Division of Endocrinology and Metabolism, Department of Internal Medicine, E-DA Cancer Hospital/I-Shou University, Kaohsiung, Taiwan

Abstract

Glomerular hyperfiltration predisposes nephron susceptible to damage irreversibly, thereby playing an important role in initiating the development of diabetic kidney disease. The pathogenesis of glomerular hyperfiltration in the past clinical trials has emphasized the importance of neurohormones such as the renin-angiotensin-aldosterone system (RAAS). Unfortunately, diabetic kidney damage or glomerular hyperfiltration does not completely get attenuated by RAAS blockade. Therefore, many recent clinical trials have focused on role of renal tubular factors to the hyperfiltration state such as the sodium-glucose cotransporter. The tubular factors are acting to increase sodium reabsorption in the renal proximal tubule through sodium-glucose Cotransporter-2 as the leading cause of hyperfiltration by afferent arteriole dilation via the tubuloglomerular feedback. Clinical evidence has suggested that sodium-glucose cotransporter-2 inhibitors (SGLT2i) can not only reduce development but attenuate deterioration of albuminuria through various mechanisms. This review aims to discuss the role of SGLT2i in type 2 diabetes patients with chronic kidney disease in detail. (J Intern Med Taiwan 2021; 32: 322-332)

Key Words: Sodium-glucose cotransport-2 inhibitor; Type 2 diabetes, Chronic kidney disease; Reno-protection, Albuminuria

Introduction

The mechanism of action of sodium-glucose cotransporter-2 inhibitors (SGLT2i) based upon sodium-glucose cotransporter-2 (SGLT2) blockade in the renal proximal tubule to inhibit glucose reabsorption in the kidney and therefore lower blood sugar[1]. This is in turn accompanied by improved glycemia, blood pressure (BP) lowering, body weight reduction, and decreased albuminuria[2]. The pleiotropic effects have implicated with reducing the risk of renal outcomes and cardiovascular events in recent large-scale clinical trials of SGLT2i[3-5] and, consequently, this class of agent is now recommended as a next step after metformin for type 2 diabetes (T2D) patients with established cardiovascular disease (CVD) in the latest American and European clinical practice guidelines[6].

Reprint requests and correspondence：Dr. Kuo-Bin Tseng
Address：Division of Endocrinology and Metabolism, Department of Internal Medicine, E-DA Cancer Hospital/I-Shou University, No.1, Yida Road, Jiaosu Village, Yanchao District, Kaohsiung City 82445, Taiwan, R.O.C.

The incidence of diabetic kidney disease (DKD) is clinical particularly importance since it results in increasing cardiovascular risk and all-cause mortality[7]. Moreover, patients presenting with asymptomatic microalbuminuria or early progressive signs of chronic kidney disease (CKD), e.g., declines in estimated glomerular filtration rate (eGFR) have been scrutinized to increase in poor clinical outcomes and mortality[8,9]. Despite increasing diversity of effective treatments, those with early stage CKD may be treated insufficiently to increase the likelihood for development of more advanced stages of renal failure[10]. Thus, preventing or attenuating the progression of albuminuria in T2D by early intervention with treatments remains necessary.

The pleiotropic effects of SGLT2i

Aside from obvious benefits of plasma glucose lowering, body weight loss and BP reduction[2], SGLT2i modify hemodynamics[11-17], promote reduction in oxidative stress (OS)[18,19], advanced glycation end-products[20-22], inflammatory makers[23-27], increase diuretic actions[3-5], and activate renin angiotensin aldosterone system (RAAS)[17] . The pleiotropic effects of SGLT2i on renal benefits are discussed below.

Hemodynamic modification

Tubuloglomerular feedback (TGF) is a negative feedback system that works on the single nephron level and regulates the tone of the afferent arteriole, and thereby eGFR, to stabilize the solute and fluid load to the macula densa[11]. However, an increased reabsorption of glucose by SGLT2 in diabetes in the renal proximal convoluted tubule decreases delivery of solutes to the macula densa and in turn causes vasodilation of the afferent arteriole, which results an increased in intraglomerular pressure and subsequently facilitates the development of diabetic nephropathy. SGLT2 inhibition restore solute delivery to the macula densa with reversal of vasodilation of the afferent arteriole and in turn preserve eGFR in long term in diabetic nephropathy[12].

SGLT2i may reverse hypoxia around the renal proximal tubules, thereby mitigating hemodynamic overload via reduction in enhanced sympathetic activity[13]. Treatment with SGLT2i leads to increased hematocrit which suggests recovery of renal tubulointerstitial function in diabetes[14]. The increased hematocrit during SGLT2i therapy has generally been interpreted as indicating hemoconcentration due to the diuretic effect, although it has been reported that the risk of cerebral infarction is not increased[3,15]. However, several studies suggested that hemoconcentration due to the diuretic effect seems unlikely the leading cause of elevated hematocrit[14,16]. A possible interesting mechanism for the elevated hematocrit might be an effect of SGLT2i on red cell mass, as suggested by the transient increases in serum erythropoietin concentrations and reticulocyte count[17].

Oxidative stress, advanced glycation end products, and inflammatory effects

OS reflects excessive production of reactive oxygen species (ROS) and the suppression of ROS removal is implicated with organ damage[28]. SGLT2i reduced ROS generation, expression of monocyte chemoattractant protein-1 gene, and apoptosis of renal tubular cells via high glucose suppression[18]. SGLT2i may reduce OS though suppression of NADPH oxidase 4-derived ROS generation and inhibit proinflammatory macrophage infiltration and inflammation in DKD[19].

The accumulation of advanced glycation end-products (AGEs) might initiate diabetic macroangiopathy through receptor for AGE (RAGE), and the increase of RAGE expression could be a reason that diabetes accelerates atherosclerosis rapidly[29]. SGLT2i have been recently recognized to inhibit renal reactions of oxidation, inflammation and fibrosis in diabetic rats partly by suppression of

AGEs and RAGE axis[20]. SGLT2i appear to prevent glucotoxicity with high efficiency by reducing formation of AGEs, methylglyoxal levels and the induction of RAGE-dependent signaling[21]. Recently, SGLT2i was suggested to improve cardiac function via AGE generation reduction and oxidative damage lowering[22]. Thus, the SGLT2i-mediated inflammatory response through a reduction in AGEs-AGEs/RAGE crosstalk provide a novel mechanism to decrease diabetic complications.

The diabetic proinflammatory mediators might activate the renal proximal tubular cells to result in increased kidney injury[30]. SGLT2i might have anti-inflammatory effects by blockade of macrophage accumulation and expression of proinflammatory biomarkers[23]. Thus, SGLT2i could significantly reduce renal morphology and structural changes of diabetes, e.g., mesangial matrix expansion, endothelial fenestrations loss, glomerular basement membrane thickening, and podocyte loss[24]. SGLT2i prevented high glucose-related increases in inflammatory cytokines production most likely via blockade of glucose entry into the renal proximal tubular cell[25]. Several other studies demonstrated that diabetic patients treated with SGLT2i may reduce serum plasminogen activator inhibitor-1 levels[26]. SGLT2i may also improve insulin sensitivity and attenuate CVD risk via induced changes of serum leptin, adiponectin, and interleukin-6 [27].

Blood pressure

It has been confirmed that BP lowering attenuates not only risk of mortality and morbidity[31], but also has renoprotective effects in diabetes[32]. However, the exact mechanism(s) behind the BP-lowering effects of SGLT2i are not completely understood. SGLT2i induce sustained systolic and diastolic BP reduction, partly through minimal natriuresis and likely sympathetic tone reductions[33]. SGLT2i can induce body weight reduction[2], which is mainly due to loss of fat mass rather than lean mass[34]. By natriuretic and osmotic diuretic effects, SGLT2i could induce volume contraction[35]. SGLT2i also can lead to an improvement in vascular resistance and arterial stiffness, which is associated with improved BP[36]. The exact mechanism(s) through which SGLT2i reduces arterial stiffness are not completely understood, but may be related to improved glycemic control, body weight reduction, volume contraction as a result of osmotic diuresis or reduced OS[36]. Moreover, SGLT2i also reduce sympathetic nervous system and RAAS activity via augmented distal sodium chloride delivery to the macula densa inducing TGF, afferent arteriole narrowing and attenuated hyperfiltration, both of which are important determinants of BP[35].

Diuretic effects

The results of the Empagliflozin Cardiovascular Outcome Even Trial in Type 2 Diabetes Mellitus-Removing Excess Glucose (EMPA-REG OUTCOME)[3], the Canagliflozin Cardiovascular Assessment Study (CANVAS) program[4], and the Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58)[5] have demonstrated that the diuretic actions of SGLT2i presumably play an important role in cardioprotection. The increased urinary sodium excretion has been observed during the early phase of treatment with SGLT2i[37,38]. SGLT2i afforded a reduction in interstitial fluid and serum sodium without changing the intravascular volume by osmotic diuresis[39]. It has been speculated that the selective reduction in interstitial volume may be a unique feature of SGLT2i rather than other diuretics, which may restrict the aberrant reflex neurohumoral stimulation to induce intravascular volume depletion with traditional diuretics[40]. Moreover, SGLT2i are uricosuric, whereas traditional diuretics are related to high levels of serum uric acid, probably reflecting the different impact on cardiovascular outcomes[41]. Natriuresis is suggested to be the primary

factor associated with the SGLT2i-induced transient increases in urine volume and decreased plasma natriuretic peptide with increased plasma renin activity (PRA) may be a compensatory mechanism for subsequent urine output recovery[42]. These findings correspond to a renal physiological and adaptive mechanism to maintain overall body fluid balance following initial treatment with SGLT2i.

Renin angiotensin aldosterone system

Several animal models reported that blockade of the RAAS reduced some features of diabetic renal injury, specifically fibrosis, macrophage infiltration, and elevations in transforming growth factor-beta gene expression[43]. SGLT2i activates systemic and local RAAS activity in diabetes, suggesting hydrochlorothiazide-like physiologic effects[17]. Although the clinical implications of SGLT2i-induced RAAS-activation are not well- understood, it seems undesirable since angiotensin receptor activation clinically play a crucial role in the development of DKD. However, the activated RAAS during angiotensin- receptor blockade or angiotensin-converting enzyme inhibition would favor renoprotective pathways of the RAAS cascade, including angiotensin 1-7 production and activation of Mas and type-2-angiotensin-II receptors[44]. Clinically, empagliflozin increased significantly angiotensin II and aldosterone levels in diabetes[45]. Similarly, dapagliflozin was associated with serum aldosterone and PRA concentration elevation[17]. Moreover, it should be noted in EMPA-REG OUTCOME that 81% of participants were treated with angiotensin converting enzyme inhibitors (ACEi) or angiotensin-receptor blockers (ARB)[3]. Thus, it is tempting to speculate that SGLT2i combines with RAAS blockade may result in similar synergistic effects by combined blockade of neurohormonal and tubular factors. Further evidence will be required to investigate whether such combined strategy of dual SGLT2i and RAAS blockade has the potential to bring long-term renoprotection, in part through normalizing glomerular hyperfiltration.

Major clinical trials on renal endpoint findings

More than 40% of diabetic patients during their lifetime develop to CKD, which is the major cause accounting for the progression of end-stage renal disease (ESRD)[46,47]. Accordingly, it is necessary to recognize whether the benefits of SGLT2i might be applicable to DKD patients, and whether potential detrimental effects, in particular renal safety, are similar or different for individuals with CKD. The recent major clinical trials of SGLT2i on renal endpoint findings are discussed below.

Canagliflozin

The renoprotection of canagliflozin in DKD patients has been investigated in several studies. T2D patients with stage 3 CKD receiving canagliflozin 100mg and 300mg versus placebo had slightly less proportion of progression to albuminuria (5.1, 8.3, and 11.8%, respectively) and larger decrease in the urinary albumin/creatinine ratio (UACR) (-3.8, - 7.2 and -0.8 μg/mg, respectively) from baseline to Week 26[48]. A follow-up extension of the above-mentioned study showed that canagliflozin (100mg and 300mg) compared to placebo demonstrated decreases in eGFR (-2.1, -4.0 and -1.6 ml/min/1.73m^2, respectively) which were likely related to the diuretic effect of canagliflozin[49]. Moreover, canagliflozin (100mg and 300mg) versus placebo provided significantly median percent reductions in UACR (-16.4, -28.0, and 19.7%, respectively). The canagliflozin 300mg suggested the larger decrease in UACR, which might result from the larger eGFR decrease with this dose, whereas the canagliflozin 100mg indicated the decrease in UACR, which was related to a steadier eGFR, argues against this rationale.

Although the renal outcomes from the CANVAS program fail to reach statistical signifi-

cance, the results suggested a promising benefit of canagliflozin with the reduction of progression to albuminuria by -27% and a sustained reduction of renal composite outcomes by -40%[4]. Moreover, when using eGFR as a continuous variable, the renoprotective effect of canagliflozin continued to suggest benefit at all levels of renal function, but may be attenuated with declining renal function (p heterogeneity = 0.02 and 0.01, respectively) [50].

A secondary analysis of a clinical trial in T2D patients with metformin therapy investigated the renal effects of canagliflozin versus glimepiride[51]. Compared with glimepiride, the proportions of 30% eGFR decline endpoint were lower for the canagliflozin 100mg and 300mg groups (6.7% versus 9.7%; p=0.07, and 9.0% versus 9.7%; p=0.75), respectively. Moreover, in the subgroup analysis, the hazard ratio (HR) for the canagliflozin 100mg and 300mg groups versus glimepiride groups in patients with UACR ≥30mg/g for the 30% eGFR decline endpoint were 0.37 (p=0.03) and 0.69 (p=0.33), respectively.

More recently, the Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study investigated the renal outcomes in T2D patients with moderate to severe albuminuria[52]. The primary outcome was a composite of ESRD, doubling of the serum creatinine, or renal or cardiovascular death. The reductions of relative risk (RR) for canagliflozin group versus placebo group were -30% (p=0.00001), -34% (p<0.001), and -32% (p=0.002) for the primary outcome, renal-specific composite, and ESRD, respectively. This result provides evidence that among T2D patients with CKD, canagliflozin might reduce risk of renal failure at a median 2.62 years of follow-up.

Empagliflozin

The EMPA-REG-RENAL investigated renal effects of empagliflozin in T2D patients with stage 2-4 CKD[53]. The reductions in UACR for emapgliflozin group versus placebo group was observed in stage 2 CKD patients (empagliflozin 10mg -184.59mg/g, p=0.0831; empagliflozin 25mg -235.86mg/g, p=0.0257) and stage 3 CKD patients (-183.78mg/g, p=0.0031) at Week 52. Moreover, less proportions of stage 3 CKD patients with empagliflozin 25mg versus placebo progressed from normoalbuminuria to microalbuminuria, or from microalbuminuria to macroalbuminuria, at the end of trial (12.2% versus 22.2%, and 2.0% versus 11.4%, respectively). Importantly, more proportions of stage 3 CKD patients with emapgliflozin 25mg regressed from macroalbuminuria to microalbuminuria, or from microalbuminuria to normoalbuminuria, at the end of trial (32.6% versus 8.6%, and 27.5% versus 21.4%, respectively).

Empagliflozin compared to placebo in the EMPA-REG OUTCOME suggested reductions in incident or worsening nephropathy by -39% (p<0.001)[3]. Moreover, the RR of development of macroalbuminuria, doubling of the serum creatinine, and start of renal-replacement treatment for empagliflozin versus placebo had statistically significant reductions of -38%, -44%, and -55%, respectively. However, the rate of incident albuminuria between the treatment groups demonstrated no statistically significant difference. Moreover, a post-hoc analysis from the EMPA-REG OUTCOME suggested that empagliflozin versus placebo significantly reduced incident or worsening nephropathy by -35% in patients with history of coronary artery bypass graft (CABG) at baseline[54]. Furthermore, similar result was also observed in patients without a history of CABG.

Another exploratory analysis from the EMPA-REG OUTCOME has been described[55]. After treatment of 12 weeks, the mean placebo-adjusted ratio of UACR change from baseline with empagliflozin suggested significantly reduction in albuminuria (normoalbuminuria -7% (p=0.013), microalbu-

minuria -25% (p<0.0001), and macroalbuminuria -32% (p<0.0001)). After treatment of 164 weeks, sustained reductions in UACR were observed with empagliflozin versus placebo. The empagliflozin group experienced a sustained more regression form microalbuminuria to normoalbuminuria (HR 1.43; p<0.0001) or from macroalbuminuria to microalbuminuria or normoalbuminuria (HR 1.82; p<0.0001), and experienced a sustained less progression from normoalbuminuria to microalbuminuria or macroalbuminuria (HR 0.84; p=0.0077).

A pooling data from T2D patients with prevalent microalbuminuria or macroalbuminuria who participated in one of five randomized controlled trials (RCTs) from baseline to week 24 investigated the effect of empagliflozin on UACR[56]. Empagliflozin versus placebo significantly reduced UACR levels in patients with albuminuria (microalbuminuria -32% (p<0.001), macroalbuminuria -41% (p<0.001)), which was not largely associated with the known metabolic or systemic hemodynamic effects of this drug class.

Dapagliflozin

A pooled analysis of 11 RCTs evaluated the effects of dapagliflozin over 102 weeks in T2D patients with eGFR between 12 and 45 ml/min/1.73m^2 [57]. Dapagliflozin (5mg and 10mg) versus placebo suggested significant reduction in UACR by -47.1% and -38.4%, respectively. A post-hoc pooled analysis from two clinical trials in T2D hypertensive patients on stable ARB or ACEi therapy suggested that dapagliflozin versus placebo was associated with greater 12-week reductions in albuminuria by -33.2% [58]. Moreover, albuminuria reduction by -23.5% was also observed after multivariate adjustment.

A clinical trial assessed dapagliflozin versus placebo in T2D patients with stage 3A CKD[59]. Dapagliflozin than placebo had greater decreases from baseline in eGFR at Week 24 (-2.49 mL/min/1. 73m^2). However, eGFR recovery to baseline was observed at Week 27. The overall population on dapagliflozin didn't have reductions in mean percent changes from baseline in UACR at Week 24. However, dapagliflozin compared to placebo in patients with baseline UACR ≥30 mg/g had significantly reductions in mean percent changes from baseline at Week 4 by -30.7% (p =0.009) and at Week 12 by - 21% (p <0.001). Although dapagliflozin from Week 12 to Week 24 maintained reductions from baseline in UACR, a decrease in UACR from Week 12 to Week 24 in the placebo group made the difference versus placebo at Week 24 not significant.

In addition to albuminuria, a clinical trial further investigated changes in N-acetyl-β-glucosaminidase (uNAG) which is a marker of renal tubular damage in uncontrolled T2D patients with dapagliflozin[60]. Dapagliflozin rather than non-SGLT2i had significantly reductions in UACR and uNAG. Dapagliflozin rather than non- SGLT2i significantly increased kidney length. By multivariate analysis, dapagliflozin versus non-SGLT2i had significantly reductions in UACR. A post hoc analysis investigated the long-term effects of dapagliflozin on UACR in patients with UACR ≥30 mg/g at baseline[61]. After adjusting for multivariate, placebo-corrected reductions were observed in the dapagliflozin (10mg and 5mg) groups by -53.6% and -47.4%, respectively. The dapagliflozin groups (5mg and 10mg) versus placebo group had more regression to a lower UACR category (39.6%, 33.9%, and 15.8%, respectively) and had fewer progression to a higher UACR category (4.3%, 14.7%, and 27.3%, respectively). Overall, the dapagliflozin groups (5mg, 10mg) versus placebo group had more regression to normoalbuminuria status (18.9%, 17.8%, and 7.0%, respectively).

The renal outcomes data from DECLARE–TIMI 58 has been described[62]. Overall, the dapagliflozin group versus the placebo group had 24% reduction in incidence of the renal compos-

ite outcome (4.3% versus 5.6%, respectively). This result suggested that in T2D patients with or were at risk for atherosclerotic CVD, dapagliflozin possibly reduces the likelihood of progression of renal disease. Thus, dapagliflozin-induced improvements in glycemic control combined with other potential effects of renal benefits, may result in long-term risk reduction of kidney.

More recently, the DELIGHT study (clinicaltrials.gov NCT02547935) investigated albuminuria-lowering effect of dapagliflozin alone and together with saxagliptin in T2D patients with CKD[63]. Dapagliflozin and dapagliflozin-saxagliptin compared to placebo significantly demonstrated reductions in UACR from baseline by -21% (p=0.011) and -48.2% (p<0.0001), respectively. This beneficial profile suggested that dapagliflozin with or without saxagliptin, given ACEi or ARB additionally treatment, is a potentially attractive therapeutic option to attenuate the progressive renal disease in these patients.

Ertugliflozin

The renal effects of ertugliflozin were assessed in T2D patients with stage 3 CKD over 52 weeks[64]. In categorical analyses of the overall cohort, the ertugliflozin groups (5mg and 15mg) versus the placebo group had higher proportions of any occurrence of a decrease >30% from baseline in eGFR at week 26 and 52 (week 26: 10.3%, 8.7%, and 2.6%, respectively; week 52: 13.5%, 14.0%, and 7.3%, respectively). No data were provided, however, the authors reported that a similar proportion of patients had shifted from normoalbuminuria to microalbuminuria across the ertugliflozin groups; none shifted from normoalbuminuria to macroalbuminuria over 52 weeks.

More recently, a pooled analysis of 2 RCTs evaluated the effects of ertugliflozin (5mg and 15mg) versus non-ertugliflozin (glimepiride or placebo) on eGFR and albuminuria in T2D patients[65]. At baseline, overall mean eGFR was 88.2 ml/min/1.73m^2 and mean UACR was 11.6 mg/g. Ertugliflozin (5mg and 15mg) versus non-ertugliflozin had greater decreases from baseline in eGFR at Week 6 (-2.3, -2.7 and -0.7 ml/min/1.73m^2, respectively). However, changes in eGFR compared to non-ertugliflozin at Week 104 was 1.81 (p=0.04) and 2.10 ml/min/1.73m^2 (p=0.01) for ertugliflozin 5mg and 15mg, respectively. Moreover, ertugliflozin (5mg and 15mg) compared to non-ertugliflozin had greater reductions in UACR at Week 104 (-29% (p=0.02) and -32.7% (p=0.01), respectively) in albuminuria patients (UACR > 30 mg/g) at baseline. The initial dip in eGFR in ertugliflozin groups possibly resulted from known hemodynamic effects. Over 104 weeks, ertugliflozin than non-ertugliflozin preserved higher eGFR levels and reduced greater UACR in albuminuria patients at baseline, suggesting renal function protection.

Possible synergic effects

The temporal acute reduction in eGFR has been observed on treatment initiation with SGLT2i in several clinical studies [66]. The initial dip in eGFR of SGLT2i relates to the attenuation of SGLT2 to primary renal proximal tubular hyperreabsorption and in turn lowers glomerular hyperfiltration and subsequently preserves eGFR in long term in T2D patients [67]. In contrast to the effect of SGLT2i, RAAS blockade also has initial dip in eGFR and a significantly slower decrease long-term decline of eGFR thereafter [68]. The exact mechanism of this hemodynamic acute dip in eGFR is unclear. A physiological explanation is that RAAS blockade causes efferent arteriole vasodilation that in turn causes a reduction in intraglomerular pressure, a reduction in filtration fraction, and an acute dip in eGFR [68]. Although the initial dip in eGFR has been observed via different pathways, both SGLT2i and RAAS blockade present the potential to bring renoprotection, in part through long-term preservation of eGFR.

Future trials of renal endpoints

Based on the pleiotropic effects of SGLT2i on renal function and renal outcomes captured in analyses of this review, it is manifest that SGLT2i demonstrate the potential benefits of renoprotective effects in DKD patients. Several dedicated ongoing renal outcomes trials will provide further illuminations of the role of SGLT2i on renal endpoints in diabetic and nondiabetic patients with CKD. The DAPA-CKD (NCT03036150) will determine the effect of dapagliflozin on the progressive renal disease in diabetic or nondiabetic patients with CKD[69]. The DAPA-HF (NCT03036124) will determine the effect of dapagliflozin on time to the first occurrence of any of the components of a renal composite in chronic heart failure patients with reduced ejection fraction[70]. The EMPA-KIDNEY (NCT03594110) will investigate the effect of empagliflozin on time to clinically relevant kidney disease progression in diabetic and nondiabetic patients with established CKD in secondary outcome measures[71]. Moreover, two dedicated ongoing heart failure trials, EMPEROR-Reduced (NCT03057977)[72] and EMPEROR-Preserved (NCT03057951)[73], are also being collected to investigate cardiovascular outcome and hospitalization for heart failure. Both trials in secondary outcome measures will investigate change in eGFR from baseline, and time to first occurrence of chronic dialysis or renal transplant or sustained reduction of eGFR. Those ongoing dedicated renal outcomes trials will help shed further light on the clinical landscape of SGLT2i on renal endpoints.

Conclusion

The pleiotropic effects of SGLT2i suggest the potential renal benefits beyond blood glucose control. Much has been learned over the past years with the growing evidence in clinical trials of meaningful renal protective effects of SGLT2i but much more remains to be done. Experience from clinical practice with SGLT2i in non-diabetic subjects is currently limited. The results of future and ongoing clinical trials will help shed further light on the role of SGLT2i on renal function in diabetic and non-diabetic patients.

Conflicts of interest

No conflicts of interest associated with this manuscript to declare.

References

1. Bays H. From victim to ally: the kidney as an emerging target for the treatment of diabetes mellitus. Curr Med Res Opin 2009; 25: 671-81.
2. Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium–glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2013; 159: 262-74.
3. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373: 2117-28.
4. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017; 377: 644-57.
5. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019; 380: 347-57.
6. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2018; 61: 2461-98.
7. Afkarian M, Sachs MC, Kestenbaum B, et al. Kidney disease and increased mortality risk in type 2 diabetes. J Am Soc Nephrol. 2013; 24: 302-8.
8. Coresh J, Turin TC, Matsushita K, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. JAMA. 2014; 311: 2518-31.
9. Kim JJ, Hwang BH, Choi IJ, et al. A prospective two-center study on the associations between microalbuminuria, coronary atherosclerosis and long-term clinical outcome in asymptomatic patients with type 2 diabetes mellitus: evaluation by coronary CT angiography. Int J Cardiovasc Imaging. 2015; 31: 193-203.
10. Zhou Z, Chaudhari P, Yang H, et al. Healthcare resource use, costs, and disease progression associated with diabetic nephropathy in adults with type 2 diabetes: a retrospective observational study. Diabetes Ther. 2017; 8: 555-71.
11. Ito S, Abe K. Tubuloglomerular feedback. JPN Heart J 1996; 37: 153-63.
12. Škrtic M, Cherney DZ. Sodium–glucose cotransporter-2 inhibition and the potential for renal protection in diabetic nephropathy. Curr Opin Nephrol Hypertens 2015; 24: 96-103.

13. Sano M. Hemodynamic Effects of Sodium-Glucose Cotransporter 2 Inhibitors. J Clin Med Res 2017; 9: 457-60.
14. Sano M, Takei M, Shiraishi Y, Suzuki Y. Increased Hematocrit During Sodium-Glucose Cotransporter 2 Inhibitor Therapy Indicates Recovery of Tubulointerstitial Function in Diabetic Kidneys. J Clin Med Res 2016; 8: 844-7.
15. Gilbert RE, Krum H. Heart failure in diabetes: effects of anti-hyperglycaemic drug therapy. Lancet 2015; 385: 210-7.
16. Sano M. A new class of drugs for heart failure: SGLT2i reduce sympathetic overactivity. J Cardiol 2018; 71: 471-6.
17. Lambers Heerspink HJ, De Zeeuw D, Wie L, Leslie B, List J. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. Diabetes Obes Metab 2013; 15: 853-62.
18. Ishibashi Y, Matsui T, Yamagishi S. Tofogliflozin, a highly selective inhibitor of SGLT2 blocks proinflammatory and proapoptotic effects of glucose overload on proximal tubular cells partly by suppressing oxidative stress generation. Horm Metab Res 2016; 48: 191-5.
19. Terami N, Ogawa D, Tachibana H, et al. Long-Term Treatment with the Sodium Glucose Cotransporter 2 Inhibitor, Dapagliflozin, Ameliorates Glucose Homeostasis and Diabetic Nephropathy in db/db Mice. PLoS One 2014; 9: e100777.
20. Ojima A, Matsui T, Nishino Y, Nakamura N, Yamagishi S. Empagliflozin, an inhibitor of sodium-glucose cotransporter 2 exerts anti-inflammatory and antifibrotic effects on experimental diabetic nephropathy partly by suppressing AGEs-receptor axis. Horm Metab Res 2015; 47: 686-92.
21. Steven S, Oelze M, Hanf A, et al. The SGLT2 inhibitor empagliflozin improves the primary diabetic complications in ZDF rats. Redox biology 2017; 13: 370-85.
22. Habibi J, Aroor AR, Sowers JR, et al. Sodium glucose transporter 2 (SGLT2) inhibition with empagliflozin improves cardiac diastolic function in a female rodent model of diabetes. Cardiovasc Diabetol 2017; 16: 9.
23. Wang XX, Levi J, Luo Y, et al. SGLT2 protein expression is increased in human diabetic nephropathy SGLT2 protein inhibition decreases renal lipid accumulation, inflammation, and the development of nephropathy in diabetic mice. J Biol Chem 2017; 292: 5335-48.
24. Brosius FC, Coward RJ. Podocytes, signaling pathways, and vascular factors in diabetic kidney disease. Adv Chronic Kidney Dis 2014; 21: 304-10.
25. Panchapakesan U, Pegg K, Gross S, et al. Effects of SGLT2 inhibition in human kidney proximal tubular cells--renoprotection in diabetic nephropathy? PloS one 2013; 8: e54442.
26. Okamoto A, Yokokawa H, Sanada H, Naito T. Changes in levels of biomarkers associated with adipocyte function and insulin and glucagon kinetics during treatment with dapagliflozin among obese type 2 diabetes mellitus patients. Drugs R & D 2016; 16: 255-61.
27. Garvey WT, Van Gaal L, Leiter LA, et al. Effects of canagliflozin versus glimepiride on adipokines and inflammatory biomarkers in type 2 diabetes. Metabolism 2018; 85: 32-7.
28. Kowluru RA, Chan PS. Oxidative stress and diabetic retinopathy. Exp Diabetes Res 2007: 43603.
29. Sun M, Yokoyama M, Ishiwata T, Asano G. Deposition of advanced glycation end products (AGE) and expression of the receptor for AGE in cardiovascular tissue of the diabetic rat. Int J Exp Pathol 1998; 79: 207-22.
30. Tang SC, Lai KN. The pathogenic role of the renal proximal tubular cell in diabetic nephropathy. Nephrol Dial Transplant 2012; 27: 3049-56.
31. Brunström M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. BMJ 2016: 352: i717.
32. Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney Int 2002; 61: 1086-97.
33. Briasoulis A, Al Dhaybi O, Bakris GL. SGLT2i and mechanisms of hypertension. Curr Cardiol Rep 2018; 20: 1.
34. Cefalu WT, Leiter LA, Yoon KH, et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. Lancet 2013; 382: 941-50.
35. DeFronzo RA, Norton L, Abdul-Ghani M. Renal, metabolic and cardiovascular considerations of SGLT2 inhibition. Nat Rev Nephrol 2016; 13: 11-26.
36. Cherney DZ, Perkins BA, Soleymanlou N, et al. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. Cardiovasc Diabetol 2014; 13: 28.
37. Komoroski B, Vachharajani N, Feng Y, Li L, Kornhauser D, Pfister M. Dapagliflozin,a novel, selective SGLT2 inhibitor, improved glycemic control over 2 weeks in patients with type 2 diabetes mellitus. Clin Pharmacol Ther. 2009; 85: 513-9.
38. Heise T, Jordan J, Wanner C, et al. Pharmacodynamic effects of single and multiple doses of empagliflozin in patients with type 2 diabetes. Clin Ther 2016; 38: 2265-76.
39. Hallow KM, Helmlinger G, Greasley PJ, McMurray JJV, Boulton DW. Why do SGLT2i reduce heart failure hospitalization? A differential volume regulation hypothesis. Diabetes Obes Metab 2018; 20: 479-87.
40. Verma S, McMurray JJ. SGLT2i and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia 2018; 61: 2108-17.
41. Wilcox CS, Shen W, Boulton DW, Leslie BR, Griffen SC. Interaction between the sodium-glucose-linked transporter 2 inhibitor dapagliflozin and the loop diuretic bumetanide in normal human subjects. J Am Heart Assoc 2018; 7: e007046.
42. Tanaka H, Takano K, Iijima H, et al. Factors Affecting Canagliflozin-Induced Transient Urine Volume Increase in Patients with Type 2 Diabetes Mellitus. Adv Ther 2017; 34: 436-51.
43. Taira M, Toba H, Murakami M, et al. Spironolactone exhibits direct renoprotective effects and inhibits renal renin–angiotensin–aldosterone system in diabetic rats. Eur J pharmacol 2008; 589: 264-71.
44. Muskiet MH, van Raalte DH, van Bommel EJ, Smits MM,

Tonneijck L. Understanding EMPA-REG OUTCOME. Lancet Diabetes Endocrinol 2015; 3: 928-9.
45. Cherney DZI, Perkins BA, Soleymanlou N, et al. Renal hemodynamic effect of sodium–glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation 2014; 129: 587-97.
46. Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease challenges, progress, and possibilities. Clin J Am Soc Nephrol. 2017; 12: 2032-45.
47. Thomas MC, Cooper ME, Zimmet P. Changing epidemiology of type 2 diabetes mellitus and associated chronic kidney disease. Nat Rev Nephrol 2016; 12: 73-81.
48. Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab 2013; 15: 463-73.
49. Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes mellitus and chronic kidney disease. Diabetes Obes Metab 2014; 16: 1016-27.
50. Neuen BL, Ohkuma T, Neal B, et al. Cardiovascular and renal outcomes with canagliflozin according to baseline kidney function: data from the CANVAS Program. Circulation 2018; 138: 1537-50.
51. Heerspink HJ, Desai M, Jardine M, Balis D, Meininger G, Perkovic V. Canagliflozin slows progression of renal function decline independently of glycemic effects. J Am Soc Nephrol 2017; 28: 368-75.
52. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019. DOI: 10.1056/NEJMoa1811744.
53. Barnett AH, Mithal A, Manassie J, et al. & EMPA-REG RENAL trial investigators. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2014; 2: 369-84.
54. Verma S, Mazer CD, Fitchett D, et al. Empagliflozin reduces cardiovascular events, mortality and renal events in participants with type 2 diabetes after coronary artery bypass graft surgery: subanalysis of the EMPA-REG OUTCOME® randomised trial. Diabetologia 2018; 61: 1712-23.
55. Cherney DZ, Zinman B, Inzucchi SE, et al. Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial. Lancet Diabetes Endocrinol 2017; 5: 610-21.
56. Cherney D, Lund SS, Perkins, BA, et al. The effect of sodium glucose cotransporter 2 inhibition with empagliflozin on microalbuminuria and macroalbuminuria in patients with type 2 diabetes. Diabetologia 2016; 59: 1860-70.
57. Dekkers CC, Wheeler DC, Sjöström CD, Stefansson BV, Cain V, Heerspink HJ. Effects of the sodium–glucose cotransporter 2 inhibitor dapagliflozin in patients with type 2 diabetes and Stages 3b–4 chronic kidney disease. Nephrol Dial Transplant 2018; 33: 2005-11.
58. Heerspink HJL, Johnsson E, Gause-Nilsson I, Cain VA, Sjöström CD. Dapagliflozin reduces albuminuria in patients with diabetes and hypertension receiving renin-angiotensin blockers. Diabetes Obes Metab 2016; 18: 590-7.
59. Fioretto P, Del Prato S, Buse JB, et al. & DERIVE Study Investigators. Efficacy and safety of dapagliflozin in patients with type 2 diabetes and moderate renal impairment (chronic kidney disease stage 3A): the DERIVE Study. Diabetes Obes Metab 2018; 20: 2532-40.
60. Sugiyama S, Jinnouchi H, Kurinami N, et al. Impact of Dapagliflozin Therapy on Renal Protection and Kidney Morphology in Patients With Uncontrolled Type 2 Diabetes Mellitus. J Clin Med Res 2018; 10: 466-77.
61. Fioretto P, Stefansson BV, Johnsson E, Cain VA, Sjöström CD. Dapagliflozin reduces albuminuria over 2 years in patients with type 2 diabetes mellitus and renal impairment. Diabetologia 2016; 59: 2036-9.
62. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019; 380: 347-57.
63. Pollock C, Stefansson B, Reyner D, et al. Albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycaemic control in patients with type 2 diabetes and chronic kidney disease (DELIGHT): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2019; 7: 429-41.
64. Grunberger G, Camp S, Johnson J, et al. Ertugliflozin in patients with stage 3 chronic kidney disease and type 2 diabetes mellitus: the VERTIS RENAL randomized study. Diabetes Ther 2018; 9: 49-66.
65. Cherney D, Heerspink HL, Frederich R, et al. Two-Year Effects of Ertugliflozin on Renal Function. Diabetes 2019 Jun; 68 (Suppl 1): https://doi.org/10.2337/db19-1197-P.
66. Nespoux J, Vallon V. SGLT2 inhibition and kidney protection. Clin Sci 2018; 132: 1329-39.
67. Vallon V, Thomson SC.Targeting renal glucose reabsorption to treat hyperglycaemia: the pleiotropic effects of SGLT2 inhibition. Diabetologia 2017; 60: 215-25.
68. Holtkamp FA, De Zeeuw D, Thomas MC, et al. An acute fall in estimated glomerular filtration rate during treatment with losartan predicts a slower decrease in long-term renal function. Kidney Int 2011; 80: 282-7.
69. ClinicalTrials.gov. A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (Dapa-CKD)-NCT03036150. 2017. https://clinicaltrials.gov/ct2/show/NCT03036150. Accessed February 1, 2018.
70. AstraZeneca [Internet]. Study to evaluate the effect of dapagliflozin on the incidence of worsening heart failure or cardiovascular death in patients with chronic heart failure (Dapa-HF). ClinicalTrials.gov record: NCT03036124; 2018 cited 2018 Jul 31. https://clinicaltrials.gov/ct2/show/NCT03036124?term=NCT03036124.
71. ClinicalTrials.gov. A Multicentre International Randomized Parallel Group Double-blind Placebo-controlled Clinical Trial of EMPAgliflozin Once Daily to Assess Cardio-renal Outcomes in Patients With Chronic KIDNEY Disease (EM-

PA-RENAL)-NCT03594110 2018. https://clinicaltrials.gov/ct2/show/NCT03594110. Accessed January 31, 2019.
72. Boehringer Ingelheim [Internet]. Empagliflozin outcome trial in patients with chronic heart failure with reduced ejection fraction (EMPEROR-Reduced). ClinicalTrials.gov record: NCT03057977; 2018 cited 2018 Jul 31. https://clinicaltrials.gov/ct2/show/NCT03057977?term=NCT03057977.
73. Boehringer Ingelheim [Internet]. Empagliflozin outcome trial in patients with chronic heart failure with preserved ejection fraction (EMPEROR-Preserved). ClinicalTrials.gov record: NCT03057951; 2018 cited 2018 Jul 31. https://clinicaltrials.gov/ct2/show/NCT03057951?term=NCT03057951.

以第２型鈉-葡萄糖共同轉運蛋白抑制劑來治療第二型糖尿病慢性腎衰竭病人之臨床面貌：我們現在的定位在哪裡與我們能夠期待的是什麼？

曾國賓

義大癌治療醫院　內科部內分泌暨新陳代謝科
義守大學醫學院

摘　要

腎小球高過濾狀態使得腎元不可逆地容易受到損傷，因此，在啟動糖尿病慢性腎臟病的發展中扮演一個重要的角色。腎小球高過濾狀態在過去的臨床研究中強調的是神經激素之重要性，例如腎素-血管收縮素-醛固酮系統。可惜的是藉由阻斷腎素-血管收縮素-醛固酮系統，糖尿病腎臟損傷或腎小球高過濾狀態並無法完全有效獲得緩解。因此，近來許多的臨床研究集中在腎小管因素對高過濾狀態之影響，例如鈉-葡萄糖共同轉運蛋白。腎小管因素是作用透過第２型鈉-葡萄糖共同轉運蛋白在腎臟近曲小管來增加對鈉離子的再吸收，藉由腎小管腎絲球回饋機制導致入球小動脈的擴張是造成其高過濾狀態的主要原因。臨床證據顯示第２型鈉-葡萄糖共同轉運蛋白抑制劑透過各種機轉不但能減少蛋白尿且能緩解蛋白尿的惡化。本篇綜論旨在詳細探討第２型鈉-葡萄糖共同轉運蛋白抑制劑在第二型糖尿病慢性腎衰竭病人治療中所扮演的角色。