Sodium Glucose Co-transporter 2 Inhibitors

By Christos Argyropoulos

Reducing the human and financial burden of progressive diabetic kidney disease (DKD) and ESKD stalled after the landmark trials of renin-angiotensin system inhibitors (RASi) in the early 2000s. The recent introduction of sodium glucose co-transporter 2 inhibitors (SGLT-2i) appears to reverse 20 years of stagnation in this area. This short review summarizes the key findings in this emerging success story of nephrology therapeutics.

Of rodents …

According to the Brenner hypothesis (1), hyperfiltration drives nephrons to glomerulosclerosis and eventually leads to chronic kidney disease (CKD) and ESKD. Reducing hyperfiltration has been the major paradigm for slowing the progression of CKD through RASi. However, the actual mechanisms of hyperfiltration in DKD remained poorly defined until the seminal report that a phlorizin, a naturally occurring SGLT-2i found in the unripe apple, inhibited glomerular hyperfiltration in the diabetic rat (2). The hypothesis was put forward that stimulation of tubular glucose/sodium transport through the SGLT-2 system reduced tubuloglomerular feedback, decreasing hyperfiltration in DKD. Subsequent micropuncture studies provided evidence in support of this hypothesis under long-term SGLT-2i administration and in diabetic mice lacking the SGLT-2 transporter (3, 4). In similar studies, SGLT-2i prevented changes in BP, glomerular size, and markers of inflammation (5).

… and humans

The U.S. Food and Drug Administration (FDA) approved the first SGLT-2i in early 2013, followed by the report of the mandatory cardiovascular outcomes safety trials (Table 1) (6–9). Overall, the trials reported to date show that SGLT-2i do not raise cardiovascular risk. Two of the SGLT-2i (canagliflozin and empagliflozin) are associated with clinically meaningful reductions in major cardiovascular events and cardiovascular death. All-cause mortality was reduced by empagliflozin, and all three SGLT-2i safety trials reported reductions in congestive heart failure (CHF). In these trials, there was an impressive reduction in the risk for hard renal endpoints (ESKD, need for dialysis or doubling of serum creatinine [DSC], or death), with relative risk reductions between 40% and 24%. These reductions, along with the effects of SGLT-2i on cardiac outcomes, are much larger than those obtained with RASi (Table 1). However, renal endpoints were either secondary or exploratory in these cardiovascular safety trials, requiring further confirmation.

The first dedicated renal endpoint, double-blind, randomized trial was recently reported for canagliflozin (CREDENCE) (10). This trial enrolled patients with estimated GFR (eGFR) between 30 and 90 mL/min per 1.73 m^2, on a background of RASi therapy. The composite endpoint of ESKD/DSC or renal death was lowered by 34%, and the relative risk of ESKD was lower by 32%. The canagliflozin group also had a lower risk of cardiovascular death, myocardial infarction, or stroke and CHF (Table 1). Importantly, there were no differences in rates of amputation or fracture, safety signals that had been reported in previous studies.

Examination of the slope of the eGFR over time shows that the SGLT-2i conform to the pattern anticipated from the Brenner hypothesis and verified in the RASi era: An initial decline over the first couple of months of therapy is followed by dramatically reduced loss of eGFR over time (10, 11). Viewed as a class, SGLT-2i also reduce BP by 2.46 mm Hg

(systolic) and 1.46 mm Hg (diastolic) while also reducing body weight by 1.88 kg and waist circumference by 2.89 cm (12).

SGLT-2i in nephrology practice

The American Diabetes Association (ADA) guidelines (13) recommend that SGLT-2i with documented cardiovascular benefit (to date, empagliflozin and canagliflozin) should be the second agent added after metformin in patients with type 2 diabetes (T2D) and CKD or CHF. This recommendation is in alignment with the FDA-approved indications for these two agents (Table 2). Currently four SGLT-2i have been approved in the United States (Tables 2 and 3); they are similar in many regards but also different in others (e.g., status of completed trials, heterogeneity in renal and cardiovascular outcomes, dosing recommendations, intrarenal handling, and an emerging, highly technical literature about off-target effects).

A suggested pragmatic approach to how these agents may be introduced into nephrology practice follows: The ADA guidelines (a live document updated throughout the year) should be consulted for the currently approved indications for SGLT-2i. As nephrologists, we want to reduce cardiorenal risk in our patients, not just lower the hemoglobin A1c, so SGLT-2i with proven benefit should be prescribed, not merely recommended, by our specialty first (Table 2). Nevertheless, the inclusion of drugs in formularies does not always follow the clinical evidence, and the clinician will often have to choose between any SGLT-2i or no SGLT-2i at all. In these situations, one should opt for the SGLT-2i whose more robust evidence the insurance will cover and the patient can afford the copay for. For optimal effect, these agents should be added on the background of RASi therapy (CREDENCE), yet, even RASi-intolerant patients can benefit, as shown in the large subgroup (20%) of the cardiovascular safety trials who

Table 1. Composite renal and cardiovascular safety outcomes of the approved (May 2019) SGLT-2 inhibitors reported in cardiovascular safety (EMPAREG, CANVAS program, DECLARE-TIMI-58) and dedicated renal outcomes trials (CREDENCE) against ACEi and ARBs in patients with diabetes

Angiotensin receptor blockers		SGLT-2 inhibitors		
Composite renal outcome				
Irbesartan (IDNT)	Losartan (RENAAL)	Canagliflozin (CREDENCE CANVAS program)	Dapagliflozin (DECLARE-TIMI-58)[9]	Empagliflozin (EMPA-REG)[7,11]
0.80 (0.66–0.97)	0.84 (0.72–0.98)	0.66 [10] (0.53–0.81) 0.60 [8] (0.47–0.77)	0.76 (0.67–0.87)	0.61 (0.53–0.70)
ESKD / Need for Renal Replacement Therapy (RRT)/DSC				
All ARB	0.78 [14] (0.67–0.91)	0.68 [10] (0.54–0.82)	0.76 (0.67–0.87)	0.45 (0.40–0.75)
All ACEi	0.60 [14] (0.39–0.93)			
MACE 3 outcome (cardiovascular death, myocardial infarction, ischemic stroke)				
All ARB	0.94 [15] (0.85–1.01)	0.80 [10] (0.67–0.95)	0.93 (0.84–1.03)	0.86 (0.74–0.99)
All ACEi	0.86 [15] (0.77–0.95)	0.86 [8] (0.75–0.97)		
Dapagliflozin				
Death of any cause				
All ARB	0.94 [15] (0.82–1.08)	0.83 [10] (0.68–1.02)	0.93 (0.82–1.04)	0.68 (0.57–0.82)
All ACEi	0.87 [15] (0.78–0.98)	0.87 [8] (0.74–1.01)		
Cardiovascular death				
All ARB	1.21 [15] (0.81–1.80)	0.78 [10] (0.61–1.00)	0.98 (0.82–1.17)	0.62 (0.49–0.77)
All ACEi	0.83 [15] (0.70–0.99)	0.87 [8] (0.74–1.01)		
Congestive heart failure				
All ARB	0.70 [15] (0.59–0.82)	0.61 [10] (0.47–0.80)	0.73 (0.61–0.88)	0.65 (0.50–0.85)
All ACEi	0.81 [15] (0.71–0.93)	0.67 [8] (0.52–0.87)		

Outcomes as reported in cardiovascular safety (EMPAREG, CANVAS program, DECLARE-TIMI-58) and dedicated renal outcomes trials (CREDENCE) against ACEi and ARBs in patients with diabetes. The definitions of the composite renal outcomes differed among trials : IDNT and RENAAL (development of ESKD), Doubling of Serum Creatinine (DSC) or death from any cause, CREDENCE (ESKD, DSC, or death from renal or cardiovascular causes), CANVAS (40% reduction in eGFR, need for renal replacement therapy (RRT) or death from renal causes), EMPAREG (progression to macroalbuminuria, DSC, RRT, renal death, and incident albuminuria; this composite outcome was not prespecified in EMPA-REG but need for RRT was), DECLARE-TIMI-58 (40% reduction in eGFR, ESKD, or death from renal or cardiovascular causes). Data on ACEi/ARB from studies in patients with both type 1 and 2 diabetes, whereas all SGLT-2i studies are in patients with diabetes type 2.

Abbreviations: ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; DSC = doubling of serum creatinine; eGFR = estimated GFR; RRT = renal replacement therapy; SGLT-2i = sodium glucose cotransporter-2 inhibitor.

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were not receiving RASi.

In contrast to the antiglycemic effect, the cardiorenal benefit appears to be dose independent, so the lowest dose of all drugs should be used. Dosing in relation to eGFR is likely to evolve over time, so the prescribing information should be consulted. The guidelines in Table 3 are likely to be modified to allow continuation of drugs even when the eGFR declines after CREDENCE. As with RASi, kidney function should be monitored periodically because these drugs have been associated with acute kidney injury (AKI). However, AKI should be clearly distinguished from the expected initial drop in kidney function, which, as with RASi, may signal a long-term benefit.

Patients should be warned about potential side effects, especially euglycemic ketoacidosis in patients already receiving insulin, and fungal genital infections. Commonsense clinical measures that may reduce the frequency (such as drying the genital area), prevent or reduce severity (instituting "sick-day" rules), or allow the early detection of these complications (e.g., providing urinary ketone strips) should be discussed with our patients. Despite the reassuring follow-up data about amputations, a thorough discussion of the risk-versus-benefit ratio should be undertaken in patients with pre-existing peripheral vascular disease.

Going forward, additional studies will report kidney and cardiac efficacy, dosing, and safety data about rare, yet sensational, side effects (e.g., amputations or Fournier gangrene) about all SGLT-2i. Given the magnitude of benefit seen in the existing trials, waiting for these future studies to conclude before we use these agents in patients with type 2 diabetes and CKD implies that we forego the opportunity to improve the care of our patients today. ■

Christos Argyropoulos, MD, FASN, is assistant professor, and division chief, nephrology, in the department of internal medicine at the University of New Mexico School of Medicine in Albuquerque, NM.

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Table 2. Indications for and pharmacologic properties of the approved (May 2019) SGLT-2 inhibitors

	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Antiglycemic indication	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Cardiovascular indication	To reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) in adults with type 2 diabetes mellitus and established CVD		To reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established CVD	
Bioavailability	65%	72%	78%	~100%
Peak plasma time	1–2 hours	2 hours (fasting) to 3 hours (fatty meal)	1.5 hours	1 hour (fasting) to 2 hours (after meal)
Protein binding	99%	91%	86.2%	93.6%
Volume of distribution	119 L	118 L	73.8 L	85 L
Half-life	10.6 hours (100 mg) to 13 hours (300 mg)	12.9 hours	12.4 hours	16.6 hours
Total body clearance	192 mL/min	207 mL/min	177 mL/min	187 mL/min
Hepatic route	>50%	21%	41.2%	40.9%
GI recovery of parent compound	41.5%	15%	>35%	33.8%
Renal route	~33%	75%	54%	50.2%
Renal recovery of parent drug	<1%	<2%	~20%	1.5%

Hepatic and renal routes of elimination refer to the recovery of radioactive labeled parent drug either as the parent drug or as one of its metabolites. None of the metabolites of the currently approved SGLT-2 inhibitors are pharmacologically active. CYP metabolism of all SGLT-2i is also minimal.

Abbreviations: CVD = cardiovascular disease; GI = gastrointestinal.

Table 3. Renal dosage adjustments for the approved (May 2019) SGLT-2 inhibitors

eGFR range	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
>60 mL/min per 1.73 m^2	100–300 mg/day	5–10 mg/day	10–25 mg/day	5–15 mg/day
45–60 mL/min per 1.73 m^2	Not to exceed 100 mg/day	5–10 mg/day	10–25 mg/day	**Not recommended**
<45 mL/min per 1.73 m^2	**Do not initiate**	**Not recommended**	**Do not initiate**	**Not recommended**
<30 mL/min per 1.73 m^2	**Contraindicated**	**Contraindicated**	**Do not initiate**	**Contraindicated**

Abbreviation: eGFR = estimated GFR.

Emergence of GLP-1 Receptor Agonists as a Therapy for Diabetic Kidney Disease

By Radica Z. Alicic, Emily J. Cox, and Katherine R. Tuttle

A multitude of clinical effects beyond glycemic control have placed glucagon-like peptide-1 (GLP-1) receptor agonists front and center in the fields of diabetology, cardiology, and nephrology. These incretin-based antihyperglycemic agents reduce the risk of new or worsening kidney disease and decrease the risk of cardiovascular death and atherosclerotic events (1–5). In the wake of these findings, the American Diabetes Association Standards of Care for treatment of hyperglycemia in type 2 diabetes now state that GLP-1 receptor agonists with proven cardiovascular benefits (liraglutide > semaglutide > exenatide extended release) should be added to the therapeutic regimen if glycemic targets are not achieved with metformin, particularly in patients with atherosclerotic cardiovascular disease (6). GLP-1 receptor agonists currently approved by the United States Food and Drug Administration are liraglutide (Victoza, Saxenda), semaglutide (Ozempic), lixisenatide (Adlyxin), exenatide (Byetta) and exenatide extended-release (Bydureon, Bydureon, BCise), and dulaglutide (Trulicity). Approved combination therapies are insulin glargine/exanitide (Soliqua 100/33) and insulin degludec/liraglutide (Xultophy 100/3.6).

Evidence supporting the kidney and cardiovascular benefits of the GLP-1 receptor agonists comes from large clinical trials enrolling patients with type 2 diabetes, cardiovascular disease, chronic kidney disease (CKD), or a combination of these conditions (Figure 1).

The dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate to severe CKD (AWARD-7) clinical trial was the first to be conducted in patients with moderate to severe CKD; nearly a third of enrolled patients had stage 4 CKD (4). Dulaglutide outperformed insulin glargine, the active comparator, in achieving glycemic control in patients with type 2 diabetes and a mean estimated GFR (eGFR) of 38 ± 13 mL/min per 1.73 m^2. Over 1 year, the average eGFR decline was –3.3 mL/min per 1.73 m^2 in the insulin-treated group and –0.7 mL/min per 1.73 m^2 in both the higher-dose (1.5 mg weekly) and lower-dose (0.75 mg weekly) dulaglutide-treated groups (4). Among AWARD-7 patients with macroalbuminuria (urine-to-albumin creatinine ratio >300 mg/g) at high risk for progression of kidney disease, attenuation of mean eGFR decline was maintained (–5.5 mL/min per 1.73 m^2 in the insulin glargine group compared with –0.7 mL/min per 1.73 m^2 and 0.5 mL/min per 1.73 m^2 in the dulaglutide 0.75-mg and 1.5-mg groups, respectively). Notably, fewer patients in the higher-dose dulaglutide group reached the composite endpoint of ESRD or >40% eGFR decline in comparison with the insulin glargine group (5.2% vs. 10.8%, p = 0.038) (7).

In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) clinical trial and the Semaglutide and Cardiovascular outcomes in patients with type 2 diabetes (SUSTAIN-6) clinical trial, treatment with liraglutide or semaglutide compared with placebo resulted in fewer patients experiencing a composite cardiovascular outcome and decreased risk of CKD development and progression—benefits mainly driven by the reduction in new-onset macroalbuminuria (2, 3, 5). Similarly to AWARD-7, in patients with albuminuria as well as those with eGFR <60 mL/min per 1.73 m^2, the LEADER trial demonstrated reduction of a composite of new-onset macroalbuminuria, doubling of serum creatinine, requirement for kidney replacement therapy, and death due to kidney causes (2). Importantly, the reduction of cardiovascular events and all-cause mortality was greater in LEADER participants with eGFR <60 mL/min per 1.73 m^2 than in those with eGFR ≥60 (8). In patients with type 2 diabetes and a recent acute coronary syndrome, the addition of lixisenatide to usual care moderately reduced albuminuria, even though the rates of cardiovascular events were unaffected (1).

The mechanism by which GLP-1 receptor agonists reduce the risk of macroalbuminuria and slow eGFR decline in patients with type 2 diabetes remains to be fully elucidated. These agents favorably affect major CKD risk factors by improving control of hyperglycemia, hypertension, and excess body weight (9–11). In addition to modifying CKD risk factors, GLP-1 signaling directly promotes antioxidant, anti-inflammatory, and antifibrotic effects in the diabetic kidney (12, 13).

GLP-1 receptor agonists fill longstanding unmet needs: antihyperglycemic agents that can be used safely and effectively in patients with moderate to severe CKD, and agents that will slow eGFR decline in patients with eGFR <30 mL/min per 1.73 m^2. The encouraging results from the AWARD-7 and cardiovascular outcome trials provide hope that the GLP-1 receptor agonists will join a growing menu of agents available to tackle the burgeoning problem of CKD in type 2 diabetes. ■

Radica Z. Alicic, MD, FHM, FACP, is with Providence Health Care and the University of Washington School of Medicine. Emily J. Cox, PhD, is with Providence Health Care. Katherine R. Tuttle, MD, FACP, FASN, FNKF, is with Providence Health Care, the Kidney Research Institute, the Institute of Translational Health Sciences, and the University of Washington School of Medicine.

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