SGLT2 Inhibitors Continue to Show Kidney, Heart Benefits at Kidney Week

By Bridget M. Kuehn

Results from two major trials of sodium glucose co-transporter 2 (SGLT2) inhibitors, a class of drugs initially developed as a treatment for type 2 diabetes mellitus, add to evidence that the drugs may offer kidney-protecting benefits. The results were presented during the High-Impact Clinical Trials session at Kidney Week 2021.

The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial found that the SGLT2 inhibitor dapagliflozin provided heart and kidney benefits regardless of the cause of underlying kidney disease. Results from the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction (EMPEROR-Reduced) trial of the SGLT2 inhibitor empagliflozin showed the drug reduced serious complications from heart failure and kidney disease in patients with and without chronic kidney disease. Results from the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial were also presented during the session and suggested that finerenone, a non-steroidal mineral corticoid receptor antagonist, may reduce kidney and heart harm in patients with chronic kidney disease and diabetes, adding to the potential options for this often hard-to-treat group.

"It's an extremely exciting time in nephrology to finally have additional options for the treatment of our patients," said session co-moderator Linda Awdishu, PharmD, a professor of clinical pharmacy at the University of California, San Diego.

SGLT2s shine

Results from DAPA-CKD (1) showed dapagliflozin improved cardiovascular and kidney outcomes for patients with type 2 diabetes mellitus and chronic kidney disease, but whether the results extended to other types of chronic kidney disease were not clear, said David Wheeler, MD, professor of kidney medicine at University College London.

At Kidney Week, Wheeler presented results of a prespecified secondary analysis including 4304 participants of the DAPA-CKD trial that showed the heart and kidney benefits of dapagliflozin were consistent across all types of kidney diseases. Patients with polycystic kidney disease and immune system disease requiring immunosuppressive therapy were excluded.

"We've shown that these renal and cardiovascular mortality benefits are present regardless of the underlying cause of chronic kidney disease and regardless of the presence or absence of type 2 diabetes," Wheeler said. "Dapagliflozin was well tolerated with a safety profile that was consistent with that seen in other populations."

Wheeler noted, "Importantly, none of the nondiabetic patients developed ketoacidosis or hyperglycemia in the study." He also reported during the press briefing that they did not see an excess of amputations in patients taking the drug compared with placebo. The US Food and Drug Administration (FDA) had initially warned of a potential risk of foot and leg amputation with the SGLT2 inhibitor canagliflozin, but that warning was later removed based on newer data (2).

"Safety information from recent clinical trials also suggests that the risk of amputation, while still increased with canagliflozin, is lower than previously described, particularly when appropriately monitored," according to the FDA statement.

Rajiv Agarwal, MBBS, professor of medicine at the Indiana University School of Medicine, said he believed that SGLT2 inhibitors do not increase the risk of amputation.

"Anybody who has had a previous amputation will be at risk of a future amputation," Agarwal said. "These drugs don't enhance that risk."

Daniel Weiner, MD, associate medical director of dialysis and associate professor at Tufts University, said that during the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial of canagliflozin (3), he and his colleagues paid a lot of attention to diabetic foot wounds, something he said should be standard of care in vulnerable patient populations. "In these vulnerable populations with diabetes and kidney diseases we should be looking at feet regularly," Weiner said. He added in a follow-up interview by e-mail that he believes agents in this class of drugs have similar risk and benefit profiles.

The EMPEROR-Reduced trial (4) has previously shown that empagliflozin reduces cardiovascular death and heart failure hospitalization and slows kidney function decline in patients with heart failure with reduced ejection fraction. Now, data presented at Kidney Week and published in *Circulation* (5) show the benefits extend to patients with chronic kidney disease. The data found empagliflozin reduced the risk of cardiovascular death and heart failure hospitalization by one-quarter; reduced total heart failure hospitalizations by 30%; and reduced a composite of dialysis, transplant, and kidney death by one-half.

"Empagliflozin slows kidney function decline in patients with and without chronic kidney disease across the spectrum," said Faiez Zannad, MD, PhD, a cardiologist and professor of therapeutics at the University of Lorraine in France, during the High-Impact Clinical Trials session. Additionally, the data found the treatment was well tolerated by patients, with and without chronic kidney disease.

Diabetes options

Treatment options for patients with kidney disease and diabetes have long been limited, but the growing data on the benefits of SGLT2 inhibitors are promising. The results from FIDELIO-DKD suggest finerenone may be another promising option—if it is approved by the FDA.

In the FIDELIO-DKD trial, which was published in *The New England Journal of Medicine* (6), 5734 patients with chronic kidney disease and type 2 diabetes mellitus from 48 countries were randomized to receive either finerenone or placebo. All of the patients were treated with a renin-angiotensin system blockade prior to randomization. It found that finerenone reduced a composite of kidney failure, a sustained 40% decrease in estimated glomerular filtration rate from baseline, or death by 18%, said Agarwal, a study co-author, during a press briefing. The drug also reduced a composite of death from cardiovascular causes, nonfatal cardiac events, and hospitalization for heart failure by 14%.

"This is an exciting discovery because we've had many other [failures] in this high-risk population of patients with diabetes and chronic kidney disease," Agarwal said.

As expected, patients in the finerenone group had a higher rate of hyperkalemia compared with the placebo group (18.3% vs. 9%), but only 2.3% of patients in the finerenone group permanently discontinued this drug because of hyperkalemia compared with 0.9% in the placebo group, Agarwal said. He noted that the rate of discontinuation because of hyperkalemia was much higher with spironolactone in the AMBER trial (7).

"An ideal drug would cause no hyperkalemia, but if you look at absolute risk it's a fraction of what we saw when we used spironolactone in this vulnerable population," Agarwal said.

Too small a proportion of patients in the FIDELIO trial (4% in the placebo and 5% in the treatment group) were taking an SGLT2 inhibitor to determine what role SGLT2 inhibitors might play in combination with finerenone, Agarwal said. Wheeler noted during the press briefing that he and his colleagues saw benefits in the small proportion of patients in the DAPA-CKD trial who were taking a mineralocorticoid receptor antagonist along with dapagliflozin.

Agarwal said dual therapy with an SGLT2 inhibitor and a renin-angiotensin-aldosterone system (RAAS) inhibitor is well-established clinical practice. If finerenone were to be approved by the FDA, it might become part of a stepwise approach or as part of a triple therapy for high-risk patients.

"If we were to be [FDA] approved, then definitely you're going to individualize therapy," he said.

Among the other trials presented during the High-Impact Clinical Trials session were the following:

- A trial showing that using citrate for anticoagulation during continuous kidney replacement therapy extended filter life compared with heparin but was inconclusive regarding a mortality benefit. Heparin was associated with more bleeds, and citrate was associated with more infections (abstract FR-OR57).
- Results from the Reducing the Burden of Dialysis Catheter Complications: A National Approach (REDUCCTION) trial found a safety bundle designed to reduce catheter-related bloodstream infections did not significantly reduce these infections (abstract FR-OR56).
- A cluster randomized trial of oral protein supplementation during dialysis for patients with normal serum albumin did not find a mortality benefit for patients with normal serum albumin (abstract-FR-OR55). ■

References

1. Heerspink HJL, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020; 383:1436–1446. doi: 10.1056/NEJMoa2024816
2. US Food and Drug Administration. FDA removes boxed warning about risk of leg and foot amputations for the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR). August 26, 2020. https://www.fda.gov/drugs/drug-safety-and-availability/fda-removes-boxed-warning-about-risk-leg-and-foot-amputations-diabetes-medicine-canagliflozin
3. Perkovic V, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019; 380:2295–2306. doi: 10.1056/NEJMoa1811744
4. Packer M, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020; 383:1413–1424. doi: 10.1056/NEJMoa2022190
5. Zannad F, et al. Cardiac and kidney benefits of empagliflozin in heart failure across the spectrum of kidney function: Insights from the EMPEROR-Reduced trial. *Circulation* 2021; 143:310–321. doi: 10.1161/CIRCULATIONAHA.120.051685
6. Bakris GL, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med* 2020; 383:2219–2229. doi: 10.1056/NEJMoa2025845
7. Agarwal R, et al. Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): A phase 2, randomised, double-blind, placebo-controlled trial. *Lancet* 2019; 394:1540–1550. doi: 10.1016/S0140-6736(19)32135-X