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DAPA-CKD: SGLT2 Inhibitor Benefit Extends to Chronic Kidney Disease Without Diabetes

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Add patients with chronic kidney disease with or without diabetes to the growing list of people who get proven benefit from treatment with an SGLT2 inhibitor.

Dr Hiddo Heerspink

In the DAPA-CKD trial, treatment with the sodium-glucose cotransporter-2 (SGLT2) inhibitor dapagliflozin (*Farxiga,* AstraZeneca) cut the incidence of substantially worsened chronic kidney disease (CKD) by an average of 39% compared with placebo when added to standard treatment, with a number needed to treat of 19 to prevent one primary outcome event after a median of 2.4 years.

The level of benefit was similar in both the one-third of enrolled patients without diabetes and in the two-thirds with diabetes, showing a statistically significant 50% cut in the primary endpoint among patients without diabetes, Hiddo J.L. Heerspink, MD, reported at the virtual European Society of Cardiology (ESC) 2020 Congress.

"We found that dapagliflozin delayed the initiation of dialysis and reduced the number of deaths," regardless of diabetes status, Heerspink, from the University Medical Centre Groningen, the Netherlands, said during a press conference. "The DAPA-CKD trial has shown dapagliflozin's potential as a long-awaited new treatment for patients with chronic kidney disease."

New Era

This finding ushers in a "completely new era in chronic kidney disease management," commented Janani Rangaswami, MD, a nephrologist and cardiorenal syndrome specialist at Einstein Medical Center in Philadelphia, Pennsylvania. "It's good news" for these patients.

The results showed that dapagliflozin is the first "game-changing" drug for CKD in two decades, following the introduction of angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers, she said in an interview.

And given the consistency of the findings with the results from several other studies that documented meaningful renal protection by several different SGLT2 inhibitors, the results from this single trial also convincingly establish dapagliflozin as a standard-of-care agent to use on the types of patients the study enrolled, she added.

Representing Many Real-world Patients

The DAPA-CKD trial enrolled 4304 patients with albuminuria based on having a urinary albumin-to-creatinine ratio of at least 200 mg/g and an estimated glomerular filtration rate (eGFR) of 25 to 75 mL/min per 1.73 m^2 (with 90% of patients having an eGFR < 60 mL/min per 1.73 m^2), and 97% were receiving treatment with a renin-angiotensin system–blocking drug.

The primary endpoint was the combined rate of a drop in eGFR of at least 50% from baseline, progression to end-stage renal disease, or renal or cardiovascular death; the between-group difference in this composite was driven primarily by both preserved eGFR and prevention of end-stage renal disease.

This represents both an appropriate target population and meaningful endpoints, Rangaswami said. The study was "very representative of who we see in real-world practice," a group that likely includes "hundreds of thousands" of U.S. patients with nondiabetic CKD, she estimated.

Another notable finding was that 14% of the enrolled patients had eGFR at baseline of 25 to 29 mL/min per 1.73 m^2, pegging them as having stage 4 CKD, and the median baseline eGFR was 43 mL/min per 1.73 m^2; however, dapagliflozin treatment was as safe and effective in these patients as it was in enrolled patients with a higher level of retained renal activity.

This experience should give clinicians greater confidence about using dapagliflozin and other drugs in the SGLT2 inhibitor class in patients with substantially depressed renal function, Rangaswami said.

"We now need to be more proactive about treating patients with more advanced kidney disease who can still benefit" from dapagliflozin treatment. "The sooner you intervene the better," to slow further progression, but the new findings show "benefit even when treating patients with lower eGFRs. There is still hope to prevent or delay dialysis."

A Heart-Kidney Connection

Dapagliflozin treatment also cut all-cause mortality by a statistically significant relative 31%, and another secondary-endpoint analysis showed a statistically significant 29% relative reduction in the rate of cardiovascular death or heart failure hospitalization. This benefit was seen consistently in several prior studies of SGLT2 inhibitors but possibly was unexpected here because enrolled patients underwent no selection for a history of heart failure or any other cardiovascular disease.

But the finding shouldn't surprise because "chronic kidney disease is an independent risk factor for cardiovascular disease across the board, and especially for heart failure," noted Rangaswami.

"Heart and kidney disease is one big spectrum," and the collected experience of several trials that have now proven the efficacy of SGLT2 inhibitors among patients with heart failure with reduced ejection fraction or with CKD, regardless of their glycemic control, shows how broadly this drug class can benefit patients across the breadth of this spectrum, she said.

DAPA-CKD was funded by AstraZeneca, the company that markets dapagliflozin (Farxiga). Dr Heerspink has been a consultant to and received research funding from AstraZeneca and from several other companies. Dr Rangaswami had no disclosures.

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