Eplerenone Cut Events in Heart Failure Patients

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PARIS – The aldosterone antagonist eplerenone cut cardiovascular events and the need for hospitalization significantly across all risk levels in patients with mild heart failure, according to a subanalysis of the EMPHASIS-HF trial.

Eplerenone (Inspra) was also shown to trim troublesome and costly repeat heart failure hospitalizations in a subset of patients followed for up to 10 additional months after the pivotal, phase III trial closed, Dr. Bertram Pitt reported at the congress.

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Major Finding: Among patients with diabetes who took eplerenone, there was a 46% reduction in the primary end point of death from cardiovascular causes or heart failure hospitalization, compared with those who took placebo.

Data Source: Subanalysis of high-risk groups and follow-up analyses of the phase III EMPHASIS-HF trial.

Disclosures: Pfizer sponsored the trial. Dr. Pitt reports financial relationships with several firms excluding Pfizer. His coauthors report similar relationships including employment with Pfizer.

"Overall efficacy, no matter where we looked, was about the same, and we had the same safety," he told reporters.

EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) was stopped prematurely last spring after eplerenone in addition to standard therapy demonstrated a 37% (hazard ratio, 0.63) improvement over placebo in the primary end point of death from cardiovascular causes or heart failure hospitalization in 2,637 patients with mild New York Heart Association class II systolic heart failure (N. Engl. J. Med. 2011;364:11-21).

Among 1,597 patients who remained on double-blind therapy after study, the primary end point occurred in 21% on eplerenone and 29% on placebo (HR, 0.66), a significant difference, said Dr. Pitt of the University of Michigan, Ann Arbor.

Repeat hospitalization for heart failure was significantly reduced with eplerenone (rate ratio, 0.62).

"This suggests, to us at least, that this is going to have important cost implications and quality of life implications, as well as important implications on survival, since we know that heart failure hospitalization relates to target-organ damage and survival," he said.

The benefits of eplerenone were particularly compelling in elderly patients and those with diabetes and renal dysfunction, three high-risk populations in whom clinicians are hesitant to use adjuvant aldosterone blockade because of fears of inducing hyperkalemia, Dr. Pitt said. He pointed out that recent head-to-head data show that the aldosterone antagonist spironolactone (Aldactone) raises hemoglobin A_{1c} and cortisol levels and reduces adiponectin in patients with diabetes, whereas eplerenone does not.

When Dr. Pitt and colleagues looked at patients with diabetes in the subanalysis, the benefit was stronger than that observed in the overall EMPHASIS-HF cohort, with a 46% reduction in the primary end point (HR, 0.54).

Dr. Pitt noted that the current American Heart Association, American College of Cardiology and European Society of Cardiology guidelines for aldosterone blockade do not specify a particular agent, but look at the agents as a class.

"We believe with [these] data, that in the next guidelines there should at least be some consideration for the specific use of eplerenone, at least in the subset of patients with diabetes," he said.

Among patients with an estimated glomerular filtration rate less than 60 mL per minute per 1.73 m^2, the improvement in the primary outcome reached 38% with eplerenone over placebo.

The study excluded patients with a baseline serum potassium level above 5.0 mmol/L and estimated GFR below 30 mL per minute per 1.73 m^2 in an attempt to minimize the risk of hyper-

kalemia. Despite this, the positive results remain applicable, Dr. Pitt said in an interview.

Among elderly patients at least 75 years old, the benefit on the primary end point with eplerenone reached 34%.

Significant benefits were also observed in patients with a left ventricular ejection fraction less than 30% and with a median systolic blood pressure of less than 123 mm Hg.

As seen in the overall EMPHASIS-HF cohort, the benefits of eplerenone were accompanied by a significant increase in the incidence of serum potassium greater than 5.5 mmol/L in each of the high-risk subgroups.

However, there were no significant increases in the incidence of serum potassium above 6 mmol/L, hospitalization leading to treatment discontinuation, hospitalization for/or deaths due to hyperkalemia, or hospitalizations for worsening renal function, Dr. Pitt said.

This is going to have important implications in terms of cost, quality of life, and survival.

DR. PITT

Invited discussant Dr. Piotr Ponikowski, with the 4th Military Hospital in Wroclaw, Poland, highlighted as important the benefits of eplerenone in people with diabetes and the reduction in repeat hospitalizations. He noted that up to 50% of heart failure patients are rehospitalized and these visits are associated with significant costs and reduced quality of life and mortality. Still, aldosterone antagonists remain underutilized in heart failure patients in Europe as well as the United States.

Physicians frequently question whether clinical trial data are real, consistent, and clinically meaningful, he said. "With the presented data, we can now say that the answer to all these questions is 'yes.' " ■

View a video interview with Dr. Pitt with the QR code, or by visiting ecardiologynews.com.