Lack of Congestion Not Predictive in Acute HF

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STOCKHOLM – The absence of signs and symptoms of congestion at discharge in patients hospitalized for acute decompensated heart failure does not predict a favorable prognosis, contrary to the conventional wisdom.

A new secondary analysis of the international EVEREST trial provides an important lesson in the everyday management of acute heart failure: "The fact that a patient improves in-hospital with diuretics and other medications is not sufficient. It's not 'mission accomplished,' " Dr. Mihai Gheorghiade said at the congress.

"There is a dissociation between signs and symptoms of congestion at discharge and outcomes. In spite of having a very low congestion score, the event rate in EVEREST during 10 months of follow-up was astronomical," said Dr. Gheorghiade, professor of medicine and surgery and associate chief of cardiology at Northwestern University, Chicago.

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Dr. Mihai Gheorghiade: The event rate in EVEREST was "astronomical."

EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan) was a double-blind study that randomized 4,133 patients with worsening heart failure and a left ventricular ejection fraction of 40% or less to the oral vasopressin V2 receptor blocker tolvaptan or placebo within 48 hours of hospitalization.

Standard background therapy in both study arms included diuretics, ACE inhibitor or angiotensin II receptor blocker therapy, a beta-blocker, and an aldosterone antagonist. In the previously reported primary results, tolvaptan proved to have no benefit over placebo during a mean follow-up of 9.9 months (JAMA 2007;297:1319-31).

Dr. Gheorghiade presented a secondary analysis focusing on the 2,061 patients in the placebo arm. At randomization, following initial treatment with diuretics, these patients had a mean congestion score of 4 points based on their degree of jugular vein distention, rales, and peripheral edema.

At discharge, patients had lost a mean 2.8 kg of body weight, and 72% had a congestion score of 0 or 1. Although that appears to be a high rate of short-term treatment success, this large subgroup of patients with minimal or no signs or symptoms of congestion at discharge had a 15% all-cause mortality and a 29% rate of rehospitalization for heart failure during the next 9.9 months.

The adverse event rate was even greater in those with a higher congestion score at discharge. In the overall placebo group, all-cause mortality was 26%, with a 40% rate of rehospitalization for heart failure during follow-up.

"We're dealing with a disorder that has an event rate as high as 50%. There is no other medical condition for which patients are hospitalized and are improving with therapy that has a comparable event rate," the cardiologist observed.

The new EVEREST analysis contains an important message for clinical trialists: Using signs and symptoms of congestion as a key target for treatment during hospitalization as well as the standard end point in acute heart failure studies, as has been common until now, is a recipe for a negative trial result.

"It's very difficult to beat placebo, because placebo plus standard therapy has a tremendous effect on congestion," Dr. Gheorghiade said. "Looking for new therapies that improve signs and symp-

toms of congestion in the whole population is a waste of time unless you're dealing with special populations who don't respond to standard therapies, such as patients with low blood pressure."

Better surrogate markers than congestion are needed to guide therapy. One possibility is B-type natriuretic peptide (BNP). The mean BNP at admission in the placebo arm of EVEREST was 1,375 pg/mL. At discharge it was still markedly elevated at 948 pg/mL.

"The lesson here is that by treating the signs and symptoms of congestion, you can make patients feel much better, but even though they are now able to walk up a flight of stairs, inside, in terms of renal function and BNP, they are still very sick," he said.

Until better treatments for acute heart failure are found, the best thing physicians can do for patients is try to identify specific targets amenable to current therapies, such as renal dysfunction or myocardial ischemia, Dr. Gheorghiade said.

The EVEREST trial was sponsored by Otsuka. Dr. Gheorghiade has received research grants and/or served as a consultant to Otsuka and numerous other pharmaceutical companies. ■