Questions finally answered about Nesiritide in world's largest heart failure study

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Results from the largest acute heart failure study ever conducted have resolved safety questions raised five years ago about the acute heart failure medication nesiritide (Natrecor), but more importantly illustrate the need for comprehensive, large, real world studies of investigational agents early in the course of development of new therapies, according to researchers at the Duke Clinical Research Institute.

The results were highlighted today in the featured late-breaker sessions at the annual American Heart Association Scientific Sessions meeting.

“We can definitively say that there were no overall differences in mortality or renal side effects between the nesiritide and placebo arms,” said Adrian Hernandez, MD, associate professor of medicine at Duke University School of Medicine who led the study and presented the findings today.

“The study showed nesiritide provided a modest improvement in shortness of breath that did not reach a rigorous threshold for significance and there was no difference in reduction of rehospitalization and death over the first 30 days following treatment.”

In the spring and summer of 2005 amid significant growth in the use of nesiritide, a pair of meta-analyses that suggested serious increased risks of impaired renal function and death among patients receiving nesiritide sparked a heated national debate about the appropriateness of its use.

A panel of experts selected and led by Eugene Braunwald, MD, ultimately recommended that Scios, Inc, now a part of Johnson & Johnson, conduct a large, well-controlled outcomes study to address safety questions.

The ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) trial was initiated in 2007 to study these questions. ASCEND-HF included 7,143 patients with acute decompensated heart failure (ADHF) who were randomly assigned to add nesiritide or placebo to other drugs already being used to manage their condition, for 24 to 168 hours. The study included 398 sites in North America, Europe, Latin America and Asia Pacific.

“While pleased that this study has definitively characterized the clinical profile of this drug, the important question is why trials of this magnitude, or even greater, are not required earlier in the course of drug development,” said Robert M. Califf, MD, study co-chair and vice chancellor for clinical research at Duke University School of Medicine, and director of the Duke Translational Medicine Institute.

“Clinicians were initially told that nesiritide had a major effect on dyspnea so it was widely used soon after it came on the market. Then meta-analyses indicated that nesiritide might increase mortality and cause renal dysfunction, so its use declined dramatically."

"We now know that neither view that drove clinical practice was correct; the drug is safe, but provides only a modest benefit for dyspnea. We must understand fundamental biology better early in drug development, and then conduct adequately sized trials to understand the balance of benefits and risks. To do less does a disservice to our patients,” Califf said.

“Scios and Johnson & Johnson deserve a lot of credit for conducting the

ASCEND-HF study, for clarifying the situation related to nesiritide, and for contributing an enormous and never before available body of information related to heart failure and heart failure treatment," said Christopher O'Connor, MD, the study's co-principal investigator and director of the Duke Heart Center.

ADHF is a major health problem that causes several million hospitalizations worldwide each year. Outcomes are generally poor with data having demonstrated 30-day mortality rates over 10 percent, and rehospitalization rates over 20 percent among Medicare patients. The 2010 estimated direct and indirect cost of heart failure in the U.S. alone is $39.2 billion.

ASCEND-HF found that nesiritide was not significantly different from placebo in the primary endpoints of shortness of breath (dyspnea), measured at six and 24 hours (p=0.030 at six hours and p=0.007 at 24 hours), or rates of heart failure rehospitalizations and death during the first 30 days following treatment (9.4 percent vs. 10.1 percent, respectively, p=0.313).

Six hours after treatment, nesiritide somewhat improved dyspnea compared with placebo, with significant improvement occurring in 513 nesiritide patients (15.0 percent) and 460 placebo patients (13.4 percent). Similarly, 24 hours after treatment, slightly more patients on nesiritide reported improved dyspnea compared to placebo - 1,025 nesiritide patients (30.4 percent) compared to 935 placebo patients (27.5 percent).

Safety measures from ASCEND-HF showed that patients treated with nesiritide plus standard care had a comparable mortality rate at 30 days (3.6 percent vs. 4.0 percent, p=NS) compared to those receiving placebo plus standard care. Furthermore, there was no statistically significant or clinically relevant evidence of kidney function impairment in patients

taking nesiritide during the first 30 days (31.4 percent vs. 29.5 percent, p=NS).

“Heart failure is a very complex disease to treat, and there is a significant need for better medications for use in treatment,” said Randall C. Starling, MD, study co-investigator and head of the section of Heart Failure and Cardiac Transplant Medicine and vice chairman of Cardiovascular Medicine at Cleveland Clinic. “With the safety questions related to nesiritide having now been addressed, it could be considered an option for physicians depending on their interpretation of clinical benefit."

Provided by Duke University