Natriuretic Peptide Effective, Safe in Acute Heart Failure

BY MITCHEL L. ZOLER
Philadelphia Bureau

STOCKHOLM — A natriuretic peptide was safe and effective for treating patients with acute, decompensated heart failure in a phase II study with a total of 221 patients.

Ularitide reduced pulmonary capillary wedge pressure, improved dyspnea, and did not worsen renal function when given for 24 hours as a continuous IV infusion, Veselin Mitrovic, M.D., said at the annual congress of the European Society of Cardiology.

A synthetic form of a natriuretic peptide made in the human kidney, ularitide, "was associated with a seemingly greater hemodynamic effect than nesiritide [Natrecor], but this must be validated by a direct comparison," commented Marco Metra, M.D., a professor of cardiology at the University of Brescia (Italy).

The study, done at 19 centers in Germany, Russia and Serbia, enrolled patients with symptomatic decompensated heart failure and a pulmonary capillary wedge pressure (PCWP) of at least 18 mm Hg. They were randomized to treatment with one of three dosages of ularitide or placebo. The drug dosages were 7.5, 15, or 30 ng/kg per minute.

One primary end point was the change from baseline in PCWP after 6 hours of treatment. All three ularitide dosages resulted in significantly larger declines in PCWP, compared with placebo. In the two groups that received the largest ularitide dosages, the average drop in PCWP was about 10 mm Hg, reported Dr. Mitrovic, medical director of the research unit at the Kerckhoff Clinic in Bad Nauheim, Germany.

The second primary end point was patients' self-assessed improvement in dyspnea after 6 hours of treatment. About 45% of the patients who received either of the two highest dosages reported a moderate or marked improvement in their dyspnea, compared with 38% who reported this degree of improvement on the lowest dosage, and 25% with this level of improvement in the placebo group.

Ularitide also produced a dose-related increase in the cardiac index and a reduction in systemic vascular resistance.

The drug had no detectable impact on urine output, serum creatinine level, or creatinine clearance. The apparent absence of an effect on kidney function may mean that ularitide acts differently from nesiritide. Evidence from a metaanalysis published earlier this year indicated that a single dose of nesiritide worsens renal function in some patients with acute, decompensated heart failure (Circulation 2005;111:1487-91).

In the new study, treatment with ularitide was associated with fewer serious adverse events and fewer deaths, compared with the placebo group. The short- and long-term effects of ularitide must be examined further in larger studies that allow assessment of morbidity and mortality events as the primary end points, Dr. Metra said.

The new results did not establish the optimal ularitide dosage, Dr. Mitrovic said. The 30 ng/kg per minute dosage may be best suited for patients with a relatively high systemic blood pressure at baseline, he said. A lower dosage, such as 15 ng/kg per minute, might work best for patients with a lower systemic blood pressure at the start of treatment.

The study was sponsored by Protein Design Labs, which holds worldwide development and marketing rights for ularitide. ■

Hypothermia Risky in Heart Failure

BY MITCHEL L. ZOLER
Philadelphia Bureau

STOCKHOLM — Body temperature may be a cheap and easy way to gauge the prognosis of patients hospitalized for heart failure, according to a retrospective analysis of data from more than 300 patients.

Patients hospitalized for heart failure and who had hypothermia (a body temperature of 96.5° F) at the time of admission were nearly fourfold more likely to die during follow-up than were patients who were normothermic at admission, Mihai Gheorghiade, M.D., said at the annual congress of the European Society of Cardiology.

"This is the first report [of a hypothermia–prognosis link], so we need to be careful. It needs validation before making any conclusion that temperature is a prognostic factor," said Dr. Gheorghiade, professor of medicine at Northwestern University, Chicago.

It is also unclear what physiologic process might link hypothermia with an increased risk of death among heart failure patients. Some possible explanations are that hypothermia reflects reduced cardiac output, neurohormonal activation, or an inflammatory response, or hypothermia may result from socioeconomic factors that also may exacerbate heart failure, said Dr. Gheorghiade, who is also with Northwestern's division of cardiology.

The correlation was made by reviewing data collected in a study designed to test the safety and efficacy of tolvaptan, an oral vasopressin receptor antagonist, in patients with systolic dysfunction who were hospitalized for worsening heart failure.

Of the 319 patients enrolled in the study, body temperature readings on admission were available for 315. Of those patients, 32 had hypothermia, with an average body temperature of 95.9° F. The other 283 patients had an average temperature of 97.7° F.

During the 60 days following hospital admission, mortality was 9.4% in the patients with hypothermia and 5.9% in those who were normothermic at admission. When investigators adjusted for baseline differences in blood urea nitrogen, age, and tolvaptan treatment, the patients with hypothermia were 3.9 times more likely to die than were patients with no hypothermia.

"I think that from now on, in clinical trials of heart failure, we should carefully measure body temperature at admission and also day after day to correlate temperature with worsening heart failure," Dr. Gheorghiade said. ■

BiDil Cuts Costs, Boosts Survival in Heart Failure

BY DAMIAN McNAMARA
Miami Bureau

BOCA RATON, FLA. — The cost of fixed-dose isosorbide dinitrate and hydralazine is more than offset by decreases in health care resource utilization by African Americans with moderate to severe heart failure, according to a poster presented at the annual meeting of the Heart Failure Society of America.

Primary end points of the African Americans Heart Failure Trial (A-HeFT) were death, first hospitalization for heart failure, and change in quality of life (N. Engl. J. Med. 2004;351:2049-57).

Heart failure costs were 6% lower: 'The drug provided a $533 cost savings with 23 additional days of survival, an astounding increase in survival.'

In addition, the researchers collected enough data to assess the economic impact of the drug combination and other factors during the trial.

"We looked at all resource utilization," Walter T. Linde-Zwirble said in an interview. "There is, nowadays, an economic story, not just a clinical story," with new medications.

"A therapy has to decrease the cost of care or provide enough of a definable outcome at an acceptable price," said Mr. Linde-Zwirble, a consultant hired by Nitromed Inc., the makers of fixed-dose isosorbide dinitrate and hydralazine (BiDil).

"Knowing it's a study sponsored by industry, I took every possible bias against the drug into account," explained Mr. Linde-Zwirble, who is vice president and chief science officer at ZD Associates in Perkasie, Pa.

The researchers calculated hospital costs according to length of stay, gender, and hospital survival by using 2003 Medicare data adjusted to 2004 dollars. They estimated background care, such as unscheduled physician and emergency department visits, by using average payments for a 5% sample of patients in the Medicare Part B database.

Medication costs were estimated by using average wholesale prices from the 2004 Red Book. The cost of fixed-dose isosorbide dinitrate and hydralazine included the manufacturer's announced price of $1.80 per tablet, the average prescribed dose, and compliance data from the A-HeFT.

"The only things that made a big difference were the costs of hospitalizations and the cost of BiDil," Mr. Linde-Zwirble said. Treatment was associated with a smaller number of hospitalizations and shorter hospital stays.

The heart failure costs—including the cost of the drug combination—were 6% lower in the treatment group, compared with the placebo group.

"The drug provided a $533 cost savings with 23 additional days of survival, an astounding increase in survival," Mr. Linde-Zwirble said.

"The more you use the intervention on appropriate patients, the more money you will save," Mr. Linde-Zwirble said. "Cardiologists 5 years from now will have a good idea of how BiDil fits in—it's still new." ■

Sleep Apnea Linked to Family History of Premature CAD Death

VANCOUVER, B.C. — Individuals with obstructive sleep apnea are more than twice as likely to have a family history of premature coronary artery disease mortality as are those without the sleep disorder, Apoor S. Gami, M.D., reported at a meeting sponsored by the International Academy of Cardiology.

This strong association between obstructive sleep apnea (OSA) and familial premature CAD mortality is independent of traditional CAD risk factors. Since a family history of early mortality due to coronary artery disease is itself a powerful independent risk factor for CAD, it's clear that patients with OSA are at increased cardiovascular risk, regardless of their traditional risk factor profile, added Dr. Gami of the Mayo Clinic, Rochester, Minn.

The cardiologist presented a cross-sectional study involving 588 subjects who underwent diagnostic polysomnography and were interviewed in detail about their family history of CAD. Of the 588 patients, 316 were diagnosed with OSA on the basis of an apnea-hypopnea index score of more than five events per hour on polysomnography.

The prevalence of a family history of premature CAD mortality—defined as death prior to age 55 in men and age 65 in women—was 11.6% in the subgroup with OSA but only 6.0% in those without the sleep disorder.

After adjustment for obesity, gender, and a personal history of CAD, patients with OSA had a 2.1-fold increased risk of having a family history of premature CAD mortality.

—Bruce Jancin