No Rise in In-Hospital Mortality With Nesiritide

BY MITCHEL L. ZOLER
Philadelphia Bureau

MADRID — Patients with acute decompensated heart failure who were treated with nesiritide had an in-hospital mortality rate that appeared to be no worse than that of patients who were treated intravenously with either nitroglycerin or a diuretic, according to data from a registry with more than 100,000 patients.

The findings "warrant prospective confirmation of the mortality risk associated with different therapies for acute decompensated heart failure," Dr. Maria Rosa Costanzo said at the annual meeting of the International Society for Heart and Lung Transplantation.

"We did not find any signal of increased [in-hospital] mortality in patients treated with either nesiritide or nitroglycerin," said Dr. Costanzo in an interview. The results of her analysis "confirm the appropriateness of nesiritide treatment in patients for whom it's approved," specifically single-dose treatment of patients with acute decompensated heart failure and symptoms that lead to hospitalization for heart failure, said Dr. Costanzo, medical director of the Edward Hospital Center for Advanced Heart Failure in Naperville, Ill.

Nesiritide's safety for treating patients with heart failure has been under a cloud since a pair of metaanalyses were published last year that suggested that patients who were treated with a single dose of the drug had an excess rate of worsening renal function and death during the subsequent 30 days.

At least one expert who reviewed the new report found limited reassurance in the findings. "The analyses appear to be well done, and they provide some comfort about the short-term safety of nesiritide," said Dr. Barry M. Massie in an interview. But the results "are not very helpful because they were only able to examine the in-hospital phase," and there was no information on renal function or length of hospital stay. The results from other studies with nesiritide have indicated that the excess of worsening renal failure occurred primarily after 7 days, and the trends toward increased mortality were most apparent after 30 days, said Dr. Massie, professor of medicine at the University of California, San Francisco, and chief of cardiology at the San Francisco Veterans Affairs Medical Center.

The new analysis used data from the Acute Decompensated Heart Failure National Registry (ADHERE), which collected data from more than 180,000 patients who were hospitalized at any of 263 participating hospitals in the United States during October 2001 to March 2006, when the registry closed. The analysis by Dr. Costanzo and her associates used data collected from nearly 135,000 patients who were enrolled through August 2004.

The ADHERE registry was sponsored by Scios Inc., the division of Johnson & Johnson that markets nesiritide (Natrecor). Dr. Costanzo serves on the scientific advisory board of Scios.

The analysis excluded about 35,000 patients from the registry who turned out not to have heart failure, had a delayed diagnosis, or had complicating conditions such as a respiratory infection or MI.

Data collected on the remaining 99,963 patients were further refined using two analytic tools aimed at simulating a prospective, controlled study.

The first tool categorized patients by their "intended primary treatment (IPT)," a method used to "simulate an intention-to-treat analysis," said Dr. Costanzo in an interview. The IPT was whichever drug or drugs a patient received during the first 2 hours of treatment. By this criterion, the vast majority of patients, more than 74,000, received an intravenous diuretic alone as their IPT. Monotherapy with nesiritide as the IPT occurred in 1,855 patients, intravenous nitroglycerin monotherapy was the IPT in 1,590 patients, and 2,465 patients received an inotrope (dobutamine, dopamine, or milrinone) as monotherapy IPT. The remaining patients received at least two drugs during their first 2 hours of treatment.

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DR. COSTANZO

Comparisons of the IPT groups were then made using a propensity analysis, a method that matches patients from two unrandomized groups by a variety of demographic and clinical characteristics. In this case, the propensity analysis used more than 55 variables, said Dr. Costanzo. Patients who could not be matched with patients from the comparator group were excluded from the analysis.

"The problem with observational data sets is that most physician-determined interventions are not random and reflect something about the judgment of risk and therefore are confounded by the resulting biases. Propensity-score matching is the favored approach to deal with confounding but is limited by only being able to deal with measured variables," commented Dr. Massie.

The two main analyses that Dr. Costanzo presented compared the in-hospital mortality rates of patients treated with nesiritide or a diuretic, and those of patients treated with nitroglycerin or a diuretic.

In the first comparison, the mortality rate was 3.6% among 1,701 patients treated with nesiritide and 4.8% among 8,505 patients treated with a diuretic, a statistically significant difference. In the second comparison, in-hospital mortality occurred in 2.7% of 1,488 patients treated with nitroglycerin compared with a 3.0% mortality rate among 7,440 patients treated with a diuretic, a difference that was not statistically significant.

Another analysis focused on patients who received either nesiritide or nitroglycerin as a second drug sometime after the initial 2-hour window that was used to define the IPT. The 1,028 patients who received nesiritide as a second drug (following initial treatment with a diuretic, nitroglycerin, or an inotrope) had an in-hospital mortality rate of 3.4%. By comparison, 1,028 patients who received nitroglycerin as a second drug had a mortality rate of 6.2%, a statistically significant difference.

Data like these are useful, Dr. Costanzo said in an interview, because following publication of the two metaanalyses a year ago, physicians have become more reluctant to prescribe nesiritide to patients with acute decompensated heart failure. "Many physicians have reverted back to using more inotropes, which I'm pretty confident are associated with increased mortality," she said. ■

β-Blocker Found Ineffective in Children With Heart Failure

BY BRUCE JANCIN
Denver Bureau

ATLANTA — Carvedilol proved no better than placebo in the first-ever randomized trial of any therapy for chronic heart failure in children, Dr. Robert E. Shaddy said at the annual meeting of the American College of Cardiology.

Until now, treatment of pediatric heart failure has been based largely on the findings of the landmark heart failure trials in adults, with anecdotal best-guess extrapolation in regard to dosing in children. β-Blocker therapy is standard in adult heart failure. But the results of this first multicenter study emphasize that heart failure in children and adults are in some ways very different conditions, added Dr. Shaddy, professor of pediatric cardiology at the University of Utah, Salt Lake City.

He reported on 161 children with symptomatic systolic heart failure who participated in a 26-center double-blind trial in which they were randomized to one of the following regimens: twice-daily placebo, carvedilol at 0.2 mg/kg b.i.d. to a maximum of 12.5 mg per dose in children weighing more than 62.5 kg, or carvedilol at 0.4 mg/kg b.i.d. to a maximum of 25 mg per dose.

The participants had dilated cardiomyopathy or congenital heart disease. Their median age was 3 years, with a range of 3 months to 17 years. All were on an ACE inhibitor unless they were intolerant. Of the total, 71% had New York Heart Association class II heart failure and 27% had class III disease at baseline, with a median left ventricular ejection fraction of 26%.

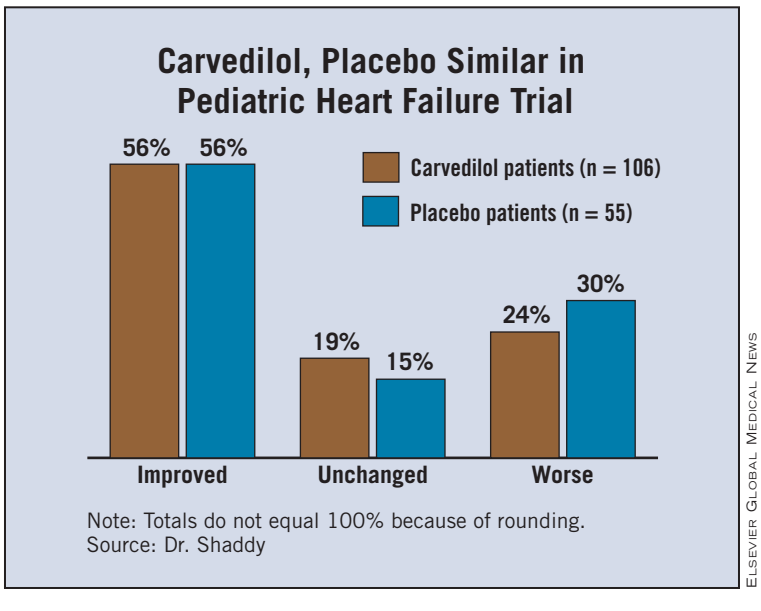
The primary study end point was heart failure outcome at 8 months as defined by a composite including death, cardiovascular hospitalization, and change in NYHA class, Ross classification of heart failure, and/or physician global assessment score. The results proved similar in the placebo and combined carvedilol groups because of an unexpectedly robust improvement in the placebo group. (See box.)

In hindsight, this might have been predicted because many think that spontaneous improvement is more frequent in younger children with heart failure—and 45% of the trial participants in this trial were younger than 2 years.

A prespecified secondary analysis showed differential results for β-blocker therapy based on ventricular anatomy. In patients with a systemic left ventricle, the rate of improvement was 51% with placebo and 64% with carvedilol. By contrast, the 41 patients with a systemic ventricle other than the left ventricle had a 64% rate of improvement with placebo, compared with 35% with carvedilol.

But it would be difficult to pursue this finding through further controlled trials restricted to children with a systemic left ventricle. Many parents, physicians, and institutional review boards have reservations about randomizing children with heart failure to placebo, said Dr. Shaddy, who is a consultant to GlaxoSmithKline, which sponsored the trial.

Discussant Dr. JoAnn Lindenfeld said that although this was a negative study, she was impressed with the trends for reduction in the objective end points of death and cardiovascular hospitalization with carvedilol, even though the trends didn't reach statistical significance. Dr. Lindenfeld is professor of medicine at the University of Colorado, Denver. ■



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