

# Drug Order Shown Irrelevant for Heart Failure

BY MITCHEL L. ZOLER  
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STOCKHOLM — A  $\beta$ -blocker and an ACE inhibitor, the two mainstays of heart failure treatment, can be started in either order and be safe and effective, according to results from more than 1,000 patients.

Until now, treatment of patients with heart failure usually began with an ACE inhibitor or an angiotensin-receptor blocker, primarily for historic reasons: ACE inhibitors were proven effective for treating heart failure first. But results from a head-to-head trial now show that both options are equivalent. An ACE inhibitor or a  $\beta$ -blocker can be started first, followed by the other drug, and patients have similar outcomes, Ronnie Willenheimer, M.D., reported at the annual congress of the European Society of Cardiology.



treatment based on individual judgment of each patient," said Dr. Willenheimer, a cardiologist at University Hospital Malmö (Sweden). "For patients with tachycardia or ischemic cardiomyopathy, I'd start with a  $\beta$ -blocker," he told this newspaper.

Dr. Willenheimer has received honoraria from the German division of Merck, which sponsored the study and markets a formulation of the  $\beta$ -blocker bisoprolol (Concor) that is approved in many countries (but not the United States) for treating heart failure. In the United States, generic bisoprolol and its trade formulation (Zebeta) are approved only for treating hypertension.  $\beta$ -Blockers approved for treating heart failure in the United States are carvedilol (Coreg) and metoprolol succinate (Toprol-XL).

The study enrolled 1,010 patients aged 65 years or older (the mean age was 72 years) with New York Heart Association class II or III heart failure at 128 centers in 20 countries. Their average left ventricular ejection fraction was 29%. Patients were randomized to start treatment with either 1.25 mg of bisoprolol once daily or 2.5 mg of the ACE inhibitor enalapril b.i.d. Their monotherapy dosage was increased every 2 weeks until the bisoprolol dosage was 10 mg once daily or the enalapril dosage was 10 mg b.i.d. Monotherapy was continued to a total duration of

6 months, after which the second drug was begun with a similar up-titration scheme. Patients were followed for an average of 1.2 years.

By all efficacy measures used, the bisoprolol-first strategy was not inferior to the enalapril-first regimen. The study's primary end point was the time to first all-cause death or all-cause hospitalization. During follow-up on an intention-to-treat basis, these events occurred in 35.2% of patients in the bisoprolol-first arm and in 36.8% of those in the enalapril-first arm. On a per-protocol basis, the event rates were 32.4% in the bisoprolol-first patients and 33.1% in the enalapril-first group (Circulation 2005;112:2426-35).

The incidence of treatment-related adverse events was also similar in both groups. However, in patients treated with bisoprolol first, the results showed a trend toward an improved survival benefit and a trend toward a higher frequency of worsening heart failure requiring hospitalization, especially early in the study.

These findings are probably class effects, Dr. Willenheimer said. In both treatment groups, the drug that was started first was given in higher dosages during the combined therapy phase. The study was limited by several factors, Dr. Dickstein noted. It was done on an open-label basis, it did not include patients with class IV disease, and patients were maintained on monotherapy for the relatively long period of 6 months. Nonetheless, he said that on the basis of the results, he believes that the two strategies probably have comparable efficacy and safety. ■

**A physician can start treatment based on individual judgment of each patient.**

DR. WILLENHEIMER

"I think this will possibly change practice. The data support using a  $\beta$ -blocker first in selected patients," commented Kenneth Dickstein, M.D., a cardiologist at the University of Bergen (Norway). "It remains a clinical question [as to] who should get a  $\beta$ -blocker first and who should first get an ACE inhibitor or angiotensin-receptor blocker."

"The results suggest free choice. A physician can start

## Nesiritide Doesn't Affect Renal Function in Stable HF Patients

BY DAMIAN McNAMARA  
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BOCA RATON, FLA. — The brain natriuretic peptide, nesiritide, which is used to treat acute heart failure symptoms, did not facilitate diuresis or protect renal function in a small study of stable hospitalized patients.

Many clinicians believe nesiritide (Natrekor, Scios Inc.) facilitates furosemide diuresis and prevents renal dysfunction, Margaret M. Redfield, M.D., said in an interview. However, a recent metaanalysis indicated that the agent might actually increase the risk of renal dysfunction (Circulation 2005;111:1487-91).

To sort it out, Dr. Redfield and her associates studied 65 patients who were hospitalized for decompensated heart failure and who were treated with a standard dose of nesiritide for relief of their heart failure symptoms. They were randomized to nesiritide as a 2-mcg/kg bolus at admission and a 0.01-mcg/kg per minute infusion at 48 hours (34 patients) or to standard therapy (31 patients).

The participants also received 40-mg b.i.d. intravenous furosemide if they had mild renal dysfunction at baseline, defined as a creatinine clearance of 40-60 mL/min. They received 80-mg b.i.d. intravenous furosemide if they had moderate renal dysfunction, or a creatinine clearance of 20-39 mL/min.

"We looked at nesiritide in the broader heart failure population where you don't need an acute effect," said Dr. Redfield, professor of medicine, Mayo Clinic College of Medicine, Rochester, Minn.

Approximately one-quarter of heart failure patients experience renal dysfunction during hospitalization, and the researchers sought to determine if nesiritide is protective, Dr. Redfield said during a poster session at the annual meeting of the Heart Failure Society of America.

A secondary objective was to determine if the agent could obviate the need for furosemide diuresis in some patients.

Mean baseline creatinine was 1.8 mg/dL in the nesiritide group and 1.7 mg/dL in the standard therapy group; by 48 hours, the mean changes were increases of 0.12 mg/dL and 0.07 mg/dL, respectively. Mean baseline brain natriuretic peptide level was 640 pg/mL for the nesiritide group and 538 pg/mL for the standard therapy group; by 48 hours, the mean changes were a 474 pg/mL increase in the nesiritide group and a 59 pg/mL decrease in the control group. Total furosemide use was 272 mg in the nesiritide group and 255 mg in the standard treatment group at 48 hours.

"Nesiritide causes no harm, but has no significant benefit," Dr. Redfield said. "Nesiritide did not enhance the response to furosemide. We hypothesized that nesiritide should have a beneficial effect on renal function—we didn't see that either."

Systolic blood pressure was lower in the nesiritide group at 24 hours, but not significantly different between groups by 48 hours.

"The standard dose was designed for hemodynamic effects," Dr. Redfield commented. "The next step is to look at a lower dose, which might provide renal protection." ■

## Ularitide Found Safe, Effective in HF

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, given intravenously, reduced pulmonary capillary wedge pressure, improved dyspnea, and did not worsen renal function when given to patients for 24 hours of continuous 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 human kidneys, ularitide, "was associated with a seemingly greater hemodynamic effect than nesiritide [Natrekor], 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 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. The study was done at 19 centers in Germany, Russia, and Serbia.

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 patients treated 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 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 further examined 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.

—Mitchel L. Zoler