

# Perindopril May Improve Diastolic Heart Failure

BY MITCHEL L. ZOLER  
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BARCELONA — Treatment with the ACE inhibitor perindopril appeared to help elderly patients with left ventricular diastolic dysfunction in a study with about 850 patients.

The study was plagued by underenrollment and by many patients changing medications from their assigned study regimens, and this may explain why the results failed to show a statistically significant difference in favor of perindopril for the primary end point of all-cause death or unplanned hospitalization for heart failure. But post hoc and secondary analyses of the data suggested that treatment with the ACE inhibitor led to improved patient outcomes, including fewer hospitalizations for heart failure, fewer days in the hospital, improved heart failure status, and improved exercise capacity, Dr. John G.F. Cleland reported at a joint meeting of the European Society of Cardiology and the World Heart Federation.

"These data should not be wasted due to methodologic problems; we need to understand what the data are telling us," commented Dr. Kenneth Dickstein, a cardiologist and professor of medicine at the University of Bergen in Stavanger, Norway. Agreeing with Dr. Cleland's interpretation, Dr. Dickstein concluded that the results "support a role for inhibition of the renin-angiotensin system in patients with heart failure and preserved systolic function."

This finding is important because although blockade of the renin-angiotensin system with an ACE inhibitor or angiotensin-receptor blocker is standard treatment for LV systolic dysfunction, scant data exist to prove the treatment's value in patients with preserved LV function and diastolic dysfunction. The only study to address this until now was the Candesartan in Heart Failure—Assess-

ment of Reduction in Mortality and Morbidity (CHARM) trial, specifically the CHARM-Preserved part of the study that assessed the efficacy of candesartan in patients with heart failure and a LV ejection fraction of at least 40% (Lancet 2003;362:777-81). The new findings are consistent with the CHARM-Preserved results, Dr. Dickstein said.

The Perindopril in Elderly People With Chronic Heart Failure (PEP-CHF) study enrolled patients aged 70 or older with evidence of diastolic dysfunction. The only background medication that patients had to receive was a diuretic. Patients were randomized to treatment with either 2 mg/day perindopril or placebo. The perindopril dosage was later raised to 4 mg/day if patients had no contraindication to the increased dosage.

The study was sponsored by Servier, which markets perindopril (Acenon). Dr. Cleland and his associates received payments from Servier for working on the study.

The initial statistical calculations called for enrolling about 1,000 patients into the trial, but only 852 entered the study because of slow recruitment. The average age of the enrolled patients was 75, and their average LV ejection fraction was about 65%. About three-quarters of patients had New York Heart Association class I or II heart failure.

Although 90% of patients remained on their assigned therapy after their first year in the study, after 18 months about 40% of patients had stopped their assigned regimen, which Dr. Cleland attributed to the difficulty of keeping older patients on a blinded regimen. Another problem was a much lower than anticipated event rate. The study design anticipated that 50% of patients would have the primary end point of death or heart-failure hospitalization

each year. Instead, the actual rate for this end point was 12.7%. Patients were followed for an average of 2.2 years.

For the complete follow-up period, the incidence of the primary end point had a relative rate reduction of 8% in the patients treated with perindopril, a nonsignificant difference. Perindopril treatment also failed to produce a significant reduction in unplanned hospitalizations for heart failure.

But in a post-hoc analysis that focused only on outcomes during the first year of follow-up, when most patients remained on their assigned regimen, the incidence of the primary end point was 10.8% in the perindopril group and 15.3% in the placebo group, a 31% relative reduction that was statistically significant.

Also at 1 year, the incidence of unplanned heart failure hospitalizations was reduced by 37% in the perindopril group, compared with the placebo group, also a significant difference.

The 1-year results "are probably the truth and what the study is trying to tell us," Dr. Dickstein commented.

Additional analysis of data collected in PEP-CHF indicated that patients with a serum level of N-terminal pro-brain natriuretic peptide (NT-proBNP, a marker of cardiac stress) below the median of 400 pg/mL had event rates similar to those in the normal elderly population. In contrast, patients whose level was above the median had event rates that were similar to those in patients with systolic heart failure who benefited when they were treated with perindopril. This finding suggested that NT-proBNP might be a useful marker for predicting the efficacy of ACE inhibitor treatment in patients with diastolic heart failure, Dr. Cleland said in an interview. ■

**Post hoc and secondary analyses suggested that perindopril improved patient outcomes, including fewer hospitalizations for heart failure.**

## ACE Inhibitor Plus ARB Increases Risk, Not Benefit

BY SHERRY BOSCHERT  
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SEATTLE — Adding an angiotensin receptor blocker to ACE inhibitor therapy in patients with heart failure significantly increased the risk of hypotension and renal failure, with a trend toward an increased risk for hyperkalemia, compared with ACE inhibitor therapy alone, in a meta-analysis of randomized, controlled trials, Dr. Rachid Lakhdar reported.

A previous meta-analysis of randomized, controlled studies found that combination therapy with an angiotensin receptor blocker (ARB) and an ACE inhibitor reduced hospitalizations in patients with heart failure but provided no survival benefit, he said in poster presentation at the annual meeting of the Heart Failure Society of America. The earlier meta-analysis did not analyze the safety of this drug combination.

Dr. Lakhdar and his coinvestigator, Dr. Mouaz H. Al-Mallah, both of Henry Ford Hospital, Detroit, searched the medical literature and abstracts from medical meetings and analyzed safety data from nine studies including 18,160 patients with heart failure. The incidence of side effects was low but was 25% higher in the combination therapy arms, compared with ACE inhibitor therapy alone, they reported.

Patients on combined therapy were

54% more likely to develop hypotension and twice as likely to develop worsened renal function, compared with patients on an ACE inhibitor alone. A 2.5-fold increase in risk for hyperkalemia was not statistically significant.

"Those side effects—hypotension, hyperkalemia, and renal failure—are related directly or indirectly to reduced angiotensin II formation," the investigators noted. The rates of cough and angioedema did not differ significantly between groups.

Not all the studies showed a significant increase in side effects with the combination therapy, perhaps owing to small sample size, short follow-up, or the characteristics of different drugs and doses. The longer trials found more side effects than shorter trials did, so it may be that some adverse events associated with the combination therapy would have shown up over time, Dr. Lakhdar and Dr. Al-Mallah suggested. "The presence of this excess risk, lack of a definitive survival benefit of this strategy, and the availability of other agents with proven survival benefit in heart failure in combination with ACE inhibitors suggests that the addition of an ARB to ACE inhibitor therapy should be discouraged," they said.

The investigators reported that they have no associations with the companies that make the drugs. ■

## Set Pacemaker Rate Below 90 In Heart Failure Patients

BY SHERRY BOSCHERT  
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SEATTLE — A heart rate of 90 beats per minute was detrimental in a study of pacemaker-dependent patients with heart failure, Krishnamurti Rao reported at the annual meeting of the Heart Failure Society of America.

Thirteen patients in a crossover study spent 2 months with the heart rate set at 60, 75, or 90 beats per minute (bpm), then were randomized to 2 months at one of the other settings, and then 2 months at the third of the three settings. At 90 bpm, patients had significantly lower ejection fractions and reduced exercise tolerance as measured by maximal oxygen consumption (peak  $\text{VO}_2$ ) and walked significantly shorter distances on 6-minute walk tests, compared with the periods when heart rates were set to 75 or 60 bpm.

"These findings suggest that a mild tachycardia of even 90 [bpm], when chronic, can lead to left ventricular dysfunction," said Mr. Rao, who conducted the study with associates on the faculty of the University of Maryland, Baltimore, and currently is a student at Boston University. He has no affiliation with the companies that make pacemakers or heart medications.

Patients also fared worse clinically at a setting of 90 bpm, compared with the

other two settings. Clinical deterioration caused four patients in the 90-bpm period and one patient in the 60-bpm period to discontinue that setting before the end of the 2 months. Symptoms worsened in some patients immediately upon starting the 90-bpm rate and in others several weeks after changing rates, he noted. Two patients had their rates turned down to 85 or 80 bpm 3-4 weeks into the 90-bpm period.

The study could not determine the optimal heart rate. Based on the data available, the investigators suggest that pacemaker rates should not be set at more than 75 bpm.

Mean peak  $\text{VO}_2$  at 60 bpm was 11 mL/kg per minute, at 75 bpm was 11.3 mL/kg per minute, and at 90 bpm was 9.5 mL/kg per minute. The exercise tolerance findings may even underestimate the negative effect of the 90 bpm, because one patient who deteriorated clinically was unable to exercise, he said.

Mean ejection fractions at 60 bpm were 33%, at 75 bpm were 30%, and at 90 bpm were 25%. On the 6-minute walk test, the mean distance was 938 feet at 60 bpm, 996 feet at 75 bpm, and 888 feet at 90 bpm.

Chronic use of  $\beta$ -blockers is known to improve cardiac function, though it has not been clear whether the benefits derive from their effects on heart rate or from other actions, he said. ■