BiDil Moderates Blood Pressure, Up and Down

BY BRUCE JANCIN
Denver Bureau

ATLANTA — Heart failure patients placed on fixed-dose isosorbide dinitrate–hydralazine derive similar morbidity and mortality benefits regardless of baseline blood pressure, Dr. Inder S. Anand said at the annual meeting of the American College of Cardiology.

This may be because the drug combination possesses the remarkable property of exerting differential effects on blood pressure depending on a patient's baseline blood pressure, according to a new secondary analysis of the African American Heart Failure Trial (A-HeFT).

These A-HeFT data show isosorbide dinitrate–hydralazine (BiDil) lowered blood pressure only in patients with normal or elevated baseline systolic blood pressure. In patients in the lowest quartile of baseline systolic blood pressure—those with a value of 112 mm Hg or less— BiDil actually increased systolic pressure by a mean of 6.4 mm Hg, said Dr. Anand, professor of medicine at the University of Minnesota and director of the heart failure program at the Veterans Affairs Medical Center, Minneapolis.

The new A-HeFT findings are extremely reassuring, he said. Despite the strongly positive primary results of A-HeFT and subsequent Food and Drug Administration approval of BiDil for use in African Americans with moderate to severe heart failure, many physicians have been leery of using the combination. That's because hydralazine has long been recognized to be a potent vasodilator.

There has been concern that the drug would drive blood pressure dangerously low in heart failure patients who have low baseline pressures. This worry stems from the observation that low blood pressure in heart failure patients is a significant predictor of increased morbidity and mortality—unlike in the general population, where lower is better.

A-HeFT, sponsored by NitroMed Inc., involved 1,050 African American heart failure patients randomized in a double-blind fashion to BiDil titrated to a target dose of 120 mg/day of isosorbide dinitrate plus 225 mg/day of hydralazine or to placebo, with state-of-the-art medical management. Overall, BiDil conferred a highly significant 43% reduction in mortality risk during 10 months of follow-up, compared with the 10.2% incidence in the placebo arm, and a 37% decrease in the risk of the combined end point of mortality or first hospitalization for heart failure (N. Engl. J. Med. 2004;351:2049-57).

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The new secondary analysis showed that the magnitude of the reductions in mortality and hospitalization was slightly greater, though not significantly, in patients whose baseline systolic blood pressure was below the median of 126 mm Hg than in those above the median, said Dr. Anand.

"These data suggest the combination is well tolerated by heart failure patients with low systolic blood pressure and [that] patients derive similar benefits regardless of baseline blood pressure. Because patients with low blood pressure are at the highest risk of bad outcomes, judicious use of the combination therapy in such patients is likely to lead to substantial benefit," he said.

Session cochair Dr. Peter E. Carson, of the Veterans Affairs Medical Center in Washington, commented, "The thing that physicians are particularly concerned about when I talk to them about this therapy is the low blood pressure—what will happen if the blood pressure is lowered? You clearly showed that it didn't affect them. That's obviously a very important finding."

In response to a question, Dr. Anand said hydralazine tolerability and titration were virtually identical in patients in all quartiles of baseline blood pressure. "I was surprised, really, looking at that data. I thought patients with higher blood pressure would get more vasodilation and therefore more headache, but no," he said. ■

Candesartan Ups Hyperkalemia Risk, CHARM Analysis Shows

BY BRUCE JANCIN
Denver Bureau

ATLANTA — Candesartan therapy triples the already significant background risk of potentially serious hyperkalemia in patients with heart failure, according to a new secondary analysis of the Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity (CHARM) program.

Periodic monitoring of serum potassium is therefore "critical" in heart failure patients—and not just those on candesartan, Dr. Akshay Desai said at the annual meeting of the American College of Cardiology.

"The estimate from our study is that one would expect roughly 34 excess hyperkalemic events per 1,000 candesartan-treated patients over 3 years. But with careful surveillance of serum potassium, this risk can be substantially reduced. In the trial, seven excess serious events per 1,000 patients were noted over the 3-year duration of follow-up with careful monitoring by study investigators. We feel that this represents the unavoidable risk of candesartan therapy in this population of patients," said Dr. Desai of Brigham and Women's Hospital, Boston.

To place this risk in perspective, he added, candesartan also prevented 43 cardiovascular death or hospitalization events per 1,000 patients.

The CHARM program involved 7,599 heart failure patients on standard therapy who were randomized in double-blind fashion to candesartan or placebo and followed for just over 3 years with regular monitoring of serum potassium. Candesartan resulted in a significant 16% reduction in the relative risk of the primary end point of cardiovascular death or heart failure hospitalization.

Hyperkalemia is well recognized to be a common and potentially life-threatening complication of treatment with renin-angiotensin-aldosterone system inhibitors. CHARM investigators categorized hyperkalemic events as "serious" if they posed a risk of death or hospitalization, and "concerning" if events were serious or would have become so if not detected early through the monitoring program, with subsequent dose adjustment or drug discontinuation.

The incidence of concerning hyperkalemia during the study was 1.8% in the placebo arm and 5.2% in the candesartan group. Serious hyperkalemic events occurred in 1.1% of the placebo group and 1.8% on candesartan. Of particular clinical relevance was the finding that hyperkalemic events were not confined to the period of candesartan dose titration; they occurred throughout follow-up, although the incidence was greater during titration, said Dr. Desai.

Several predictors of increased background risk of concerning hyperkalemia were identified. Age greater than 75 years, being on an ACE inhibitor or spironolactone, or a history of diabetes was associated with roughly a twofold increased risk. Baseline renal insufficiency or hyperkalemia conferred a fivefold spike in risk. Candesartan therapy was associated with a threefold increase in risk of hyperkalemia, compared with placebo—but the drug's therapeutic benefit was also consistent across all patient subgroups, including those at high baseline risk for hyperkalemia.

Dr. Gary S. Francis, director of the coronary intensive care unit at the Cleveland Clinic Foundation, called the new results "very important data that have practical implications." He asked how often potassium should be monitored.

"I would suggest, particularly in patients at high baseline risk, be quite careful to measure serum potassium within a 2- to 3-week period after every dose titration, and again intermittently—even randomly—over the course of follow-up," he said. ■

SSRIs Are Safe, Effective in Easing Depression in Heart Failure

BY MITCHEL L. ZOLER
Philadelphia Bureau

ATLANTA — Treatment with an antidepressant drug relieved the mild to moderate depression that often occurs in patients with heart failure in a controlled study with 26 patients.

But the reduction of depression symptoms using a selective serotonin reuptake inhibitor generally did not improve quality of life measures in these patients, Dr. Mark R. Vesely and his associates reported in a poster at the annual meeting of the American College of Cardiology.

The findings suggest physicians should screen for depression in patients with heart failure, then treat when depression is diagnosed, he said in an interview. Treatment with an SSRI is safe and effective. Next would be to examine whether treating depression can produce any reductions in hospitalization rates or death in heart failure patients, said Dr. Vesely, a cardiologist at the University of Maryland in Baltimore.

Results from previous studies have shown that depression occurs in 24%-48% of patients with heart failure. Despite this high prevalence, "heart failure patients usually don't get treated" for depression, said Dr. Stephen S. Gottlieb, professor of medicine and director of the heart failure service at the University of Maryland and a coinvestigator for the study.

An SSRI is the logical, first-line agent to use to treat depression in a patient with heart failure because of its presumed safety in these patients. By contrast, treatment with a tricyclic antidepressant involves the risk of producing neurohormonal activation that might exacerbate the heart failure, Dr. Vesely said.

The study included patients with New York Heart Association class II or III heart failure who were diagnosed with mild or moderate depression by a score of 10 or more on the Beck Depression Index (BDI). The average BDI score of the patients enrolled was about 21, and they were all placed on an optimal panel of heart failure medications.

The patients were randomized to treatment with either paroxetine-CR (Paxil CR) 12.5 mg daily or placebo for 12 weeks. During follow-up, three patients dropped out of the study. After 12 weeks, the BDI score fell by an average of 12 points in the 12 patients treated with paroxetine-CR for the full study, compared with an average 0.5 point rise in 11 placebo patients, a significant difference.

Quality of life was measured with several scales: the Minnesota Living With Heart Failure emotional and physical scales, and the mental and physical scales of the Short Form-36. There were no significant improvements for most of these measures in the paroxetine-treated patients compared with the controls. The sole exception was the mental score on the Short Form-36, which rose by 9 points in the actively treated patients and by 1 point in the placebo-treated patients, a significant difference.

GlaxoSmithKline, which markets Paxil CR, supplied the drug in this study. The study and investigators received no other industry support. ■