New HF Indication for Candesartan

BY ELIZABETH MECHCATIE
Senior Writer

Candesartan's heart failure indication has been expanded by the Food and Drug Administration to include patients who are on ACE inhibitor therapy.

The angiotensin receptor blocker (ARB) was approved for a narrower heart failure indication in February, for patients with New York Heart Association (NYHA) class II-IV disease and a left ventricular ejection fraction (LVEF) of 40% or less to reduce cardiovascular death and heart failure hospitalizations, based largely on the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM)-Alternative trial, in which cardiovascular death or heart failure hospitalization, the primary end point, was reduced by 23% in those on candesartan, compared with those on placebo.

In May, the FDA approved the addition of the following statement to the heart failure indication in the drug's label: "Atacand also has an added effect on these outcomes when used with an ACE inhibitor."

Candesartan, marketed as Atacand by AstraZeneca, was approved for treating hypertension in 1998. It is the first ARB approved for use with an ACE inhibitor for treating heart failure.

The latest approval was based on the results of the CHARM-Added trial, which showed that candesartan "adds a meaningful and important additional clinical benefit on top of other proven treatments, including β-blockers and ACE inhibitors," Christopher Granger, M.D., director of the cardiac care unit at Duke University, Durham, N.C., and a member of the CHARM executive committee, said in an interview.

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DR. GRANGER

The relative risk of cardiovascular mortality or heart failure hospitalization was reduced by 15% in those on candesartan during a median follow-up of 41 months in CHARM-Added, which compared candesartan to placebo in 2,548 patients with NYHA class II-IV heart failure and an LVEF of 40% or less who were on an ACE inhibitor and standard therapy. Benefits were also seen in patients treated with β-blockers, suggesting there were no adverse interactions between β-blockers, candesartan, and ACE inhibitors.

Improved quality of life was also seen in the study, said Dr. Granger, who was a consultant to AstraZeneca for the FDA's cardiovascular and renal drugs advisory committee meeting in February, where the panel unanimously recommended approval of candesartan for this population of patients on an ACE inhibitor (CARDIOLOGY NEWS, April 2005, p. 10).

The recommended starting dose of candesartan for patients with heart failure is 4 mg/day, with a target dose of 32 mg once daily, achieved by doubling the dose about every 2 weeks, as tolerated.

In the CHARM studies, rates of hypotension, abnormal renal function, and hyperkalemia were higher in those on candesartan, as expected, due to a greater degree of renin-angiotensin-aldosterone system inhibition. Clinicians should monitor for hyperkalemia and renal insufficiency, especially when starting and titrating treatment, Dr. Granger advised. ■

Low Body Temp Raises Heart Failure Mortality

WASHINGTON — Body temperature below 36° C at hospital admission was independently associated with a lower survival rate in a study of 56,659 patients with advanced heart failure.

Disordered thermoregulation is common in patients with advanced heart failure, and body temperature measurements may improve risk assessment in these patients, Brahmajee K. Nallamothu, M.D., wrote in a poster presented at the Clinical Research 2005 meeting sponsored by the American Federation for Medical Research.

Dr. Nallamothu, a cardiologist at the University of Michigan, Ann Arbor, and his associates reviewed data on patients aged 65 years and older who were participating in the National Heart Care Project.

The mean body temperature upon hospital admission was 36.5° C, and most of the patients' admission temperatures were between 36° C and 38° C. However, 10,754 (18.5%) of the patients had body temperatures below 36° C and 1,145 (1.9%) had body temperatures above 38° C.

After multivariate analysis, patients with body temperatures below 36° C had significantly higher mortality, both in hospital (adjusted risk ratio, 1.28) and at 1 year after their hospitalizations (adjusted risk ratio, 1.14). Body temperatures above 38° C were not significantly associated with in-hospital mortality, but they were significantly associated with lower mortality after 1 year (adjusted risk ratio, 0.80).

—Heidi Splete

EECP May Aid Heart Failure Patients on Optimal Therapy

BY BRUCE JANCIN
Denver Bureau

ORLANDO, FLA. — A standard 7-week course of enhanced external counterpulsation therapy in patients with heart failure who are on optimal pharmacotherapy improves their exercise duration, quality of life, and New York Heart Association class for at least 6 months afterward, according to the results of a randomized trial presented at the annual meeting of the American College of Cardiology.

"We believe these results suggest that EECP provides adjunctive therapy in patients with New York Heart Association [NYHA] class II-III heart failure receiving optimal pharmacologic therapy," said Arthur M. Feldman, M.D., chairman of the steering committee for the Prospective Evaluation of EECP in Congestive Heart failure (PEECH) trial.

PEECH involved 187 patients with systolic heart failure (HF) and a mean ejection fraction of 26% who were randomized at 29 medical centers to optimal drug therapy alone or in combination with 35 hour-long EECP sessions over 7 weeks. Patients were unblinded as to their treatment allocation, as were their treating physicians; however, a separate group of blinded investigators performed all patient evaluations, explained Dr. Feldman, professor and chairman of the department of medicine at Thomas Jefferson University, Philadelphia.

The primary end point of the study was at least a 60-second improvement in exercise duration at follow-up 6 months after the last EECP session. This was achieved in 35% of the EECP group and 25% of the control patients, a significant difference. However, there was no between-group difference in a predefined alternative primary end point, which was the percentage of patients achieving at least a 1.25-mL/kg per minute increase in peak oxygen consumption (VO_2).

Exercise duration improved by 25 seconds in the EECP group and declined by 10 seconds in controls.

DR. FELDMAN

Exercise duration improved by a mean of 25 seconds in the EECP group, whereas it declined by 10 seconds in controls. To put this 35-second difference into perspective, Dr. Feldman said that randomized trials of cardiac resynchronization therapy show it typically results in roughly a 50-second differential in exercise duration, compared with sham therapy.

Improvement in NYHA class was a secondary PEECH end point. At 6 months, 31% of the EECP patients, and only 14% of control patients showed at least a one-class improvement.

Another secondary end point was quality of life as measured in terms of change from baseline in scores on the Minnesota Living with Heart Failure questionnaire. One month after completion of the EECP sessions, treated patients had a mean 8.9-point improvement, compared with a 3.4-point gain in control patients. The quality of life advantage favoring the EECP group remained significant at 3 months, but not at 6 months.

VASOMEDICAL

In EECP therapy, ECG-synchronized cuffs inflate at diastole and deflate at systole, increasing coronary artery blood flow.

EECP treatment was well tolerated, although one patient developed a pulmonary embolism that investigators believed was therapy related.

Discussant Andrew D. Michaels, M.D., characterized the PEECH results as "mixed."

"The trial met one of two primary end points. It's somewhat concerning that the end points that were met—namely increased exercise duration, improved quality of life, and improvement in [NYHA] class—are all subject to the placebo effect," added Dr. Michaels of the University of California, San Francisco.

Dr. Feldman said that although EECP resulted in a significant gain in VO_2 in an earlier pilot study, the PEECH population may have been biased against realizing a similar benefit because they were predominantly NYHA class II and hence did not have a long way to go to reach an essentially normal response.

EECP utilizes a series of ECG-synchronized inflatable cuffs wrapped around the legs. The cuffs swiftly inflate at onset of diastole and rapidly deflate at onset of systole, providing hemodynamic effects similar to intraaortic balloon counterpulsation, including increased coronary artery blood flow along with afterload reduction.

Enhanced external counterpulsation therapy is approved for the treatment of stable angina. The average payment to physicians under Medicare is $138.34 per session.

Both Dr. Feldman and Dr. Michaels are consultants to Vasomedical Inc., which markets EECP systems and sponsored the PEECH trial. ■