Irbesartan Flops for Heart Failure in I-PRESERVE

BY CAROLINE HELWICK
Contributing Writer

NEW ORLEANS — Heart failure patients with preserved systolic function did not benefit from treatment with an angiotensin II receptor blocker, according to results of the I-PRESERVE trial, the world's largest placebo-controlled trial of an ARB.

"Disappointingly, for this large group of patients—almost half the patients with heart failure—there remains no specific evidence-based therapy," concluded Dr. Barry M. Massie, who presented the results of the Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) trial at the annual scientific sessions of the American Heart Association.

Although no pharmacologic therapy has been shown to be effective in improving outcomes in this type of heart failure, inhibitors of the renin-angiotensin-aldosterone system have been of interest because that system is involved in many of the processes associated with this syndrome, such as hypertension, left ventricular hypertrophy, myocardial fibrosis, and vascular dysfunction. Previous studies have hinted at benefits from ARBs and from ACE inhibitors, but statistically significant improvements have not been established, 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.

I-PRESERVE included 4,128 patients with class II-IV heart failure and a left ventricular ejection fraction of at least 45%. The population was similar to that seen in prior epidemiologic studies in several important ways. The patients were mostly women, were elderly (median age 72 years), and about 9 of 10 had a history of hypertension. The average left ventricular ejection fraction was 59%.

Patients were randomized to either irbesartan up to 300 mg daily or usual care (placebo). The primary end point was a composite of all-cause death, hospitalization for heart failure, myocardial infarction, unstable angina, arrhythmia, and stroke.

After a mean follow-up of approximately 4 years, the primary outcome rates were nearly identical, occurring in 36% (742 of 2,067) of the irbesartan patients and 37% (763 of 2,061) of the placebo group. Similarly, there were no significant differences in the major secondary end points of cardiovascular death and death or hospitalization due to heart failure, or in any of the eight prespecified subgroups, Dr. Massie reported.

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"Irbesartan was unsuccessful in achieving its primary or secondary outcomes," Dr. Massie announced. The results are consistent with two previous trials in patients with heart failure and preserved ejection fraction that did not show a positive treatment effect with either candesartan or perindopril, he added.

Dr. Massie acknowledged that this was a "very well treated population," with most patients receiving diuretics and many receiving other medications. "After randomization, there was an intensification of all these therapies," he observed, explaining that this can confound outcomes.

"For this field to move forward, we need a better understanding of the mechanisms underlying this syndrome, and we need to find potential targets above and beyond those used for low ejection fraction patients. We need to do something. This affects more than 2 million individuals in the United States alone."

Dr. Margaret M. Redfield, professor of medicine at the Mayo Clinic, Rochester, Minn., called I-PRESERVE, "a very important trial, if only for the fact that ARBs and ACE inhibitors are already widely used for the treatment of heart failure with preserved ejection fraction, even though no randomized trial has shown a benefit. Two huge registries have shown that 60% are treated with these agents despite the lack of evidence."

In this form of heart failure, she said there is little evidence that activation of the renin-angiotensin system is associated with disease progression, unlike in patients with reduced ejection fractions. "This may be why the trial was negative," she speculated.

She also observed that patients in I-PRESERVE were largely similar to those in observational studies, but that they had fairly normal hemoglobin levels and renal function, "which is uncommon in the elderly with heart failure," she pointed out. "Few had concentric hypertrophy, though some had concentric remodeling, and very few had advanced diastolic dysfunction or high filling pressures. So, this was a relatively healthy cohort and not as reflective of this syndrome as we would have hoped."

The study was funded by Bristol-Myers Squibb Co. and Sanofi-Aventis. The results were simultaneously published online in the New England Journal of Medicine (doi:10.1056/NEJMoa08005450). ■

Exercise Training Safe, Beneficial for Heart Failure Patients

BY CAROLINE HELWICK
Contributing Writer

NEW ORLEANS — In the largest study of exercise training as part of the management of heart failure to date, a guided exercise program was safe and modestly effective, although investigators acknowledged that patients found it hard to keep up the routine.

The safety of exercise training in heart failure patients, outside of a supervised environment, has been a concern, but this study proved benefits could be obtained without excess risk, said Dr. Christopher M. O'Connor, presenting results of the Heart Failure and A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial at the annual scientific sessions of the American Heart Association.

"Over 30 randomized trials have shown increased exercise capacity and possibly improved survival with exercise training, but these were largely single-center studies that were underpowered or lacked adequate controls and produced limited data on safety," he noted at a press conference.

HF-ACTION, a randomized, phase III trial sponsored by the National Heart, Lung, and Blood Institute, followed 2,331 heart failure patients at 82 international sites for an average of 2.5 years. The relatively young population, median age 59 years, had an average left ventricular ejection fraction (LVEF) of 25%, indicating moderate HF. History of coronary occlusion and prior myocardial infarction was common.

Patients were randomized to an exercise training program aimed at increasing workout intensity and duration or to usual care, where they were encouraged to exercise, based on the American College of Cardiology/AHA recommendations of 30 minutes of moderate exercise most days of the week. Both groups received optimized medical treatment, patient education, and follow-up phone calls.

The exercise training followed the cardiac rehabilitation model. Patients were prescribed a multistage, guided workout of 36 supervised training sessions of 30 minutes of exercise three times a week. At the 18th session, patients received a treadmill or exercise bicycle for home use, learned how to monitor their heart rate during exercise, and were encouraged to complete five weekly sessions of similar intensity and 40 minutes' duration.

At 4-6 weeks, patients were exercising a median of 95 minutes per week, a little short of the goal of 120 minutes. This was consistent for the first year and then diminished further, reported Dr. O'Connor, professor of medicine and director of the heart center at Duke University Medical Center, Durham, N.C.

The diminished adherence is not surprising, he said, because "lifestyle intervention trials are very difficult. At the completion of a drug trial, for example, 85% of patients would still be on the drug. Here, after 3 years people were exercising for about 50 minutes. We had wanted them to exercise for 120 minutes. So adherence is extremely difficult."

Exercise training was not associated with a significant reduction in the primary end point, all-cause mortality and hospitalization. Adjusted for heart failure etiology, this group experienced a 7% relative risk reduction that was not statistically significant. Secondary composite end points also failed to reach significance: cardiovascular (CV) mortality plus CV hospitalization was reduced by 8%, and CV mortality plus HF hospitalization was reduced by 13%, Dr. O'Connor reported.

However, improvements in outcomes emerged in the prespecified adjusted analysis that accounted for additional key prognostic variables related to heart failure outcomes. These included exercise duration, LVEF, Beck Depression Inventory score, and history of atrial fibrillation flutter.

In the adjusted analysis, the primary end point was significantly reduced by 11%, and CV mortality plus heart failure hospitalization was significantly reduced by 15%. The reduction in CV mortality plus CV hospitalization remained a nonsignificant 8%.

"The prespecified adjusted analysis is a fair analysis of these data and is probably closest to the truth," Dr. O'Connor maintained. "Prognostic factors are most important. The reductions in risk were in the range of 11%-15%."

The study found no excess risk for CV events or fractures with intensive exercise. "Perhaps the most important finding is that exercise training of this degree was safe," Dr. O'Connor added. There was no increase in CV events or fractures with intensive exercise.

The improvements in outcomes were obtained in a setting of excellent overall cardiac care, he added, as more than 90% of patients received evidence-based medical therapy for their disease. "We achieved an 11%-15% meaningful reduction in clinical end points above that, with a safe intervention," he emphasized.

Discussant Dr. Philip Poole-Wilson said, "This study stresses that the advice to exercise is correct and important. Now, how to persuade the patient is harder."

"The study missed the primary end point, and some would say that's the end of it. But that would be wrong," said Dr. Poole-Wilson, professor of medicine at the Imperial College London. "After adjustments, it met many end points, and this means it was a positive trial. The study supports the use of exercise and will strengthen guidelines for the treatment of heart failure, which has wide implications."

Dr. Clyde Yancy spoke to the financial implications of the study in an interview. He pointed out that the paradigm for exercise has long been established in the form of the cardiac rehabilitation model in which patients enroll in a program over 9-12 weeks to define a new lifestyle," he said. "When exercise emanates from a structured rehab program, it quadruples adherence rates.

"The important question is whether the study data are sufficient to say that enrollment in a rehab program should become an evidence-based treatment strategy in heart failure. Because if it is guideline-generated then the expectation is that CMS and payers would cover the cost," said Dr. Yancy, medical director of Baylor University, Dallas. ■