Continue Beta-Blockers in AHF Exacerbations

BY BRUCE JANCIN

BARCELONA — The common practice of discontinuing beta-blocker therapy during hospitalization for acute heart failure is counterproductive, according to a French randomized trial.

"During acute heart failure, beta-blocker therapy should be continued, because this practice is not associated with delayed or lesser improvement, and there is a higher rate of chronic beta-blocker therapy 3 months later, the benefits of which are well established," Dr. Guillaume Jondeau concluded in presenting the results of the Beta Blocker Continuation Versus Interruption in Patients With Congestive Heart Failure Hospitalized for a Decompensation Episode (B-CONVINCED) trial at the annual congress of the European Society of Cardiology.

B-CONVINCED was conducted to redress the lack of level 1 evidence regarding the best clinical strategy when patients with systolic dysfunction who are on chronic beta-blocker therapy are hospitalized for acute heart failure (AHF). Many physicians, reasoning that the failing circulatory system needs adrenergic support, halve the dose or halt the drug altogether. The 2008 ESC guidelines state as a class IIA recommendation that "a reduction in the beta-blocker dose may be necessary. In severe situations, temporary discontinuation can be considered."

B-CONVINCED, a noninferiority trial in 147 patients, hypothesized that continuing the beta-blocker would not result in worse outcomes than stoppage upon hospital admission. The primary end point was improvement in both dyspnea and general well being as assessed by blinded physicians 3 days into the hospitalization. This was achieved in 93% of the beta-blocker continuation group and 92% of the drug-halt group. Similarly, another round of blinded physician assessments after 8 days concluded 95% of patients in both study arms were significantly improved. Duration of hospital stay, patient self-assessments, and rehospitalization rates during the next 3 months were also similar in the two groups.

However, the proportion of patients on beta-blocker therapy 3 months after the acute exacerbation was significantly different: 90% in the continuation group and 76% in the discontinuation group. This reflects the reality that once beta-blocker therapy for AHF has been stopped, it can be a challenge to restart and titrate up to effective doses, said Dr. Jondeau of the University of Paris.

Discussant Karl Swedberg noted that there is a decades-long history of skepticism regarding the use of beta-blockers in heart failure. Yet today, they are the best-documented and most effective therapy for systolic heart failure.

B-CONVINCED provides the first solid randomized clinical trial evidence that sticking to the prehospitalization dose of a beta-blocker during an AHF exacerbation instead of halting the drug at admission should be the first-line strategy, said Dr. Swedberg, professor of cardiology at Sahlgrenska University Hospital, Goteborg, Sweden. "More patients will be on effective treatment at 3 months, and many lives will be saved by this strategy."

The trial was funded by the French Ministry of Health. Neither Dr. Jondeau nor Dr. Swedberg disclosed any relationships with industry. ■

Ejection Fraction Climbed 11%

Heart Failure *from page 1*

"Men got a good result, but women got twice as good a result. This is an extremely important finding. This is the largest-ever percentage of women in any device trial," said Dr. Moss, professor of medicine at the University of Rochester (N.Y.). The explanation for the gender difference isn't clear, he added.

MADIT-CRT involved 1,820 patients with an ejection fraction of 30% or less, a QRS of 130 msec or more, and New York Heart Association class I or II symptoms. All were candidates for an implantable cardioverter defibrillator (ICD), so they were randomized 3:2 to an ICD plus CRT or an ICD alone.

During an average follow-up of 2.4 years, the primary study end point of all-cause mortality or a heart failure hospitalization or other nonfatal heart failure event occurred in 17.2% of the CRT group and 25.3% of controls. This 34% relative risk reduction was entirely driven by the 41% difference in risk of heart failure events, which was largely limited to patients having a QRS duration of at least 150 msec. CRT had no impact on mortality, which was 3% per year in both groups.

Over the course of the first year, mean ejection fraction in the CRT group climbed by 11%, from 24% to 35%, compared with a 3% gain in controls. This finding further substantiates the hemodynamic improvement provided by CRT in a relatively asymptomatic population.

Discussant Günter Briethardt of University Hospital, Munster (Germany) noted that the MADIT-CRT findings were consistent with those from the 2-year follow-up of the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial reported in Barcelona 2 days earlier (CARDIOLOGY NEWS, September 2009, p. 6).

Taken together, Dr. Briethardt said, the two studies make a "relatively strong" case for broadening the guidelines to extend CRT to NYHA class II patients, not just the class III/IV patients for whom the device therapy is now indicated. However, there were too few class I patients in both studies to make the case for CRT in those patients, he added.

MADIT-CRT met with a cooler reception from American College of Cardiology President Alfred A. Bove. "I don't think this trial is going to change the practice of medicine at this point," he said in an interview.

The 41% reduction in the risk of heart failure sounds impressive, but it masks an absolute difference amounting to only 3.7% per year, noted Dr. Bove, a cardiologist at Temple University, Philadelphia.

"The CRT story is following exactly the pattern of the original ICD stuff. It looks good, but when you really dig down into the data the differences are small. When Medicare approved ICDs for patients with an ejection fraction of 35% or less and symptomatic heart failure, docs thought they'd be doing 300-400 ICD implantations a year. It did not turn out that way because when they started looking at the details they realized the therapy wasn't that much of an advantage," he said.

For him, the message from MADIT-CRT is that in counseling patients with mildly symptomatic cardiomyopathy about CRT, he'll need to inform them that only 3 out of every 100 device recipients per year will benefit in terms of heart failure events, there's no way to predict who those 3 will be, and the device therapy has a 5% complication rate. "On an individual patient basis it does not look that great."

The most impressive MADIT-CRT finding to him was the 3% annual mortality. "That's good news in a population with an ejection fraction of 24%, average age 65, with class I or II heart failure. That's pretty low. When I started treating heart failure it was three or four times that," Dr. Bove recalled.

MADIT-CRT was funded by Boston Scientific. Dr. Moss reported receiving grant support and lecture fees from the company. Dr. Briethardt disclosed that he has served on the advisory boards of several drug companies, and has received research funds from various companies through the German Atrial Fibrillation Network.

The study results were published online (N. Engl. J. Med. 2009 Sept. 1 [doi:10.1056/NEJMoa0906431]) simultaneously with Dr. Moss' presentation. ■

Novel Acute Heart Failure Drug Fails Major Test

BY BRUCE JANCIN

BARCELONA — In its pivotal phase III clinical trial for treatment of patients in acute heart failure with renal impairment, the selective adenosine A1 receptor antagonist rolofylline has failed in every respect, and Merck has announced it will discontinue the drug's development.

Rolofylline had shown promise in an earlier 301-patient pilot study, with favorable effects on dyspnea and renal function and trends for lower mortality and readmission rates than with standard therapy, Dr. Marco Metra said at the annual congress of the European Society of Cardiology.

The negative findings in a definitive study for a drug with a novel mechanism of action are a setback in the effort to find new, more effective treatments for acute heart failure. AHF is the No. 1 cause of hospitalization in patients over age 65, it carries a dismal prognosis, and there have been no significant advances in its medical treatment, he said at a press conference in which he discussed the PROTECT trial.

Most patients who are hospitalized with AHF have underlying chronic kidney disease or experience worsening renal function during their hospital stay. This is associated with a worse prognosis. Adenosine mediates diuretic resistance and worsening renal function, so rolofylline, as a selective adenosine blocker, was an attractive drug, explained Dr. Metra of the University of Brescia (Italy).

In PROTECT, 2,033 patients were randomized 2:1 to 30 mg/day of intravenous rolofylline given over 4 hours for 3 days or placebo. All participants were hospitalized with signs of fluid overload requiring intravenous loop diuretics, mild to moderate impairment of renal function, and an elevated concentration of either brain natriuretic peptide or N-terminal pro-B-type natriuretic peptide.

Seizures or stroke occurred in 1.5% of the rolofylline group, compared with 0.6% of the placebo group.

DR. METRA

The primary outcome was treatment success, defined as moderate to marked improvement in dyspnea 24 and 48 hours after the start of treatment in the absence of persistent renal impairment or other negative outcomes. This was achieved in 41% of the rolofylline group and 36% of controls, a nonsignificant difference.

The drug proved to have no impact on the roughly 15% rate of persistent renal failure, the 60-day readmission rate of just under 26%, or 60-day mortality, which was 8.9% with rolofylline and 9.5% with placebo.

Particularly concerning was the finding that seizures or stroke occurred in 1.5% of the rolofylline group, compared with 0.6% of the placebo group, said Dr. Metra, who has been a consultant and advisory board member for Merck. ■