Device Improves Scores, Short of Efficacy Goal

BY BRUCE JANCIN

ORLANDO — Cardiac contractility modulation, an innovative device therapy for advanced heart failure, significantly improved peak VO_2, quality of life scores, and New York Heart Association functional class in the randomized 50-center FIX-HF-5 trial.

"I'm extremely encouraged by the results of this study, and I think there's a future for cardiac contractility modulation. It has the potential to be a real breakthrough," Dr. William T. Abraham said at the annual meeting of the American College of Cardiology.

There's a hitch, however. The FIX-HF-5 trial did not meet its primary efficacy end point, which was achievement of at least a 20% improvement in anaerobic threshold on metabolic exercise testing. That end point, imposed by the Food and Drug Administration, has never been used as a pivotal outcome in a heart failure study, and in hindsight it was a poor choice, according to Dr. Abraham, professor of medicine, physiology, and cell biology, and director of cardiovascular medicine, at Ohio State University, Columbus.

"In other trials of metabolic exercise testing and heart failure there seems to be a disconnect between peak VO_2 and anaerobic threshold. Peak VO_2 may improve significantly with little or no change in anaerobic threshold. I just don't think it's the right measure of exercise capacity in heart failure. We'll look to use a different primary end point in our confirmatory study," he explained.

Cardiac contractility monitoring (CCM) involves implantation of a pacemaker-like device with leads to the right heart. The device, known as the Optimizer III, delivers an electrical signal during the absolute refractory period of the cardiac cycle; thus, unlike a pacemaker, the Optimizer III signal does not initiate a heartbeat. Instead, it upregulates genes involved in cardiac calcium channels to boost cardiac contractility at a lower work level, thus improving overall cardiac efficiency. The system relies on a transcutaneously charged battery, promoting long device life.

A 20% or greater improvement in anaerobic threshold occurred in 17.6% of patients receiving cardiac contractility monitoring therapy and 11.7% of controls, a nonsignificant difference.

FIT-HF-5 was an unblinded study in which 428 patients with advanced heart failure were placed on optimal medical therapy and randomized to receive the Optimizer III or not. Roughly 90% of participants were NYHA class III, the rest were class IV. The average QRS duration was 101 ms. The Optimizer III operated for 5 hours per day during the 12 months of follow-up.

A 20% or greater improvement in anaerobic threshold occurred in 17.6% of the CCM group and 11.7% of controls, a nonsignificant difference.

The real action involved the prespecified secondary end points—which in other heart failure trials with metabolic exercise testing have been the primary end points. Peak VO_2 worsened over the course of the year in controls but improved in the CCM group, with a highly significant mean difference of 0.65 mL/kg per min between the two groups.

There was also a mean 10-point difference favoring the CCM group in quality of life as measured by the Minnesota Living With Heart Failure Questionnaire. "That meets or exceeds the benefit seen with other device or drug therapies," Dr. Abraham noted.

More than 44% of the CCM group experienced at least a 1-grade improvement in NYHA functional class, which was nearly twice the rate in controls.

Roughly half of FIX-HF-5 participants were NYHA class III with a left ventricular ejection fraction of 25% or more. The magnitude of benefit with CCM seen in this subgroup exceeded that in other participants. For example, they had a mean 1.3 mL/kg per min advantage in peak VO_2 compared with controls, which is better than that seen in the controlled trials of cardiac resynchronization therapy. These are the type of patients to be enrolled in the pivotal trial now being planned, according to the cardiologist.

Discussant Clyde W. Yancy, president-elect of the American Heart Association, observed that new therapies with novel mechanisms of action are desperately needed in the field of heart failure, and said he is pleased that further studies of CCM are planned. But he sounded a note of caution.

"This is a very provocative study, but by the same token there is something about CCM that bespeaks of an inotropic effect, so we have to continue to be very thoughtful and circumspect and follow up larger populations for a longer period of time," said Dr. Yancy, medical director of the Baylor Heart and Vascular Institute, Dallas.

Dr. Abraham has received research grants and consulting fees from Impulse Dynamics, sponsor of FIT-HF-5. ■

Vagus Nerve Stimulation Shows Promise in Advanced HF

BY BRUCE JANCIN

ORLANDO — Chronic vagus nerve stimulation delivered by an implantable device resulted in significant functional and quality of life improvements in patients with advanced heart failure in a first-in-man study.

The 32-patient trial documented significant reductions in heart rate, New York Heart Association functional class, and Minnesota Living With Heart Failure scores along with increased left ventricular ejection fraction and improved 6-minute walk distance at assessment after 3 months of treatment, Dr. Gaetano M. De Ferrari reported at the annual meeting of the American College of Cardiology.

All of these benefits were maintained at the 6-month mark (see box).

"We believe that a large controlled study is now warranted," said Dr. De Ferrari, head of cardiac intensive care at San Matteo Polyclinic in Pavia, Italy.

Vagus nerve stimulation (VNS) is approved for drug-refractory epilepsy and drug-refractory depression. Dr. De Ferrari presented the first-ever experience with the therapy in heart failure patients.

The rationale for VNS as a novel therapy for heart failure lies in the observation that reduced vagal activity and increased sympathetic tone are associated with increased mortality following acute MI as well as in heart failure. Moreover, additional vagal withdrawal often precedes episodes of acute decompensated heart failure.

Animal studies conducted by Dr. De Ferrari and coworkers at the University of Pavia 2 decades ago showed that chronic VNS markedly reduced mortality in the setting of post-MI heart failure, the cardiologist reported.

VNS benefits were maintained after 6 months. 'We believe that a large controlled study is now warranted.'

DR. DE FERRARI

In the new clinical trial, 32 participants with NYHA class II-III heart failure each had an investigational CardioFit stimulator made by BioControl, an Israeli company, implanted in the right upper chest under the clavicle. The device was connected to a cuff electrode wrapped around the right cervical vagus nerve. The system is capable of sensing the R wave and delivering one or more pulse-synchronous stimuli of 0.5-msec duration. The stimulatory pulses were delivered at an average amplitude of 4.1 mAmp. The device was on an average of 21% of the time.

In this study, intended to establish safety, six patients experienced minor treatment-related adverse events such as cough, pain at stimulation site, or voice difficulties, all of which resolved with device tuning or adaptation. In addition, there were two serious device-related adverse events: a case of postoperative pulmonary edema, and a surgical revision after device implantation.

Outcomes of Vagus Nerve Stimulation

End point	Baseline	3 months	6 months
Heart rate	81.9 bpm	75.1 bpm	76.0 bpm
Six-minute walk test	410 m	470 m	471 m
LV ejection fraction	22.5%	27.7%	26.6%
Quality of life*	47.6	32.6	32.0

*Minnesota Living With Heart Failure score
Source: Dr. De Ferrari

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While there was no control group in this early study, Dr. De Ferrari dismissed the notion that the observed benefits might be due to the placebo effect.

"Most often the placebo effect lasts a few months. It's unlikely to continue for a 6-month period," he said.

He and his coworkers are now trying to pin down which patients with advanced heart failure are most likely to respond to VNS. The five diabetic patients in the study did not benefit. The best responders were patients with a slightly higher baseline heart rate and those who could tolerate more intensive vagal stimulation.

Discussant Marvin A. Konstam called chronic VNS an intriguing and promising new therapeutic approach.

"The opportunity for benefit from increasing vagal tone is multifactorial. In the very simplest of terms, just the reduction in heart rate may be beneficial. I think to this day we don't know for sure how much of the benefit of beta-blockade in heart failure may simply be heart rate reduction, so on that ground alone I think there's potential benefit. Also, there's a potential antiarrhythmic effect from increasing vagal tone," said Dr. Konstam, professor of medicine at Tufts University, Boston.

Dr. De Ferrari replied that there are several additional plausible mechanisms of benefit for chronic VNS, including anti-apoptotic and anti-inflammatory effects.

He disclosed having received research grants from, and serving as a paid consultant to, BioControl. ■