Clinical Trials Methods and Design

A Comparison of Cardiac Resynchronization by Sequential Biventricular Pacing and Left Ventricular Pacing to Simultaneous Biventricular Pacing: Rationale and Design of the DECREASE-HF Clinical Trial

DAVID B. DE LURGIO, MD,[1] ELYSE FOSTER, MD,[2] MICHAEL B. HIGGINBOTHAM, MD,[3] KINLEY LARNTZ, PhD,[4] AND LESLIE A. SAXON, MD[2]

Atlanta, Georgia; Durham, North Carolina; Minneapolis, Minnesota; Los Angeles, California; St. Paul, Minnesota

ABSTRACT

Background: The first generation of cardiac resynchronization therapy (CRT) devices approved for the treatment of heart failure used simultaneous biventricular (BiV) pacing to achieve ventricular resynchronization. Left ventricular pacing alone and sequential BiV pacing also show promise as alternative ways to deliver CRT, but have not been studied together in a large randomized trial.

Methods: The Device Evaluation of CONTAK RENEWAL 2 and EASYTRAK 2: Assessment of Safety and Effectiveness in Heart Failure (DECREASE-HF) Trial is a randomized, double-blind, 3-arm study of patients in New York Heart Association Class III or IV with an ejection fraction of 35% or less and a QRS duration $\geq$150 ms. Patients are randomized to receive either left ventricular pacing, simultaneous BiV pacing, or sequential BiV pacing.

Conclusion: The study uses a novel composite endpoint that combines peak oxygen consumption and left ventricular end systolic dimension, thus combining a measure of symptomatic improvement (peak oxygen consumption) with a physiologic measure of ventricular reverse remodeling (left ventricular end systolic dimension) into a single composite score. Additionally, the safety and effectiveness of the CONTAK RENEWAL 2/4/4HE/EASYTRAK 2 system will be evaluated using: heart failure-related adverse events; system-related complications; left ventricular lead-related complications; detection time of induced ventricular fibrillation; and left ventricular lead performance (pacing threshold, pacing impedance, and R-wave amplitude).

Key Words: Congestive heart failure, resynchronization therapy, left bundle branch block, implantable defibrillator.

Approximately 4.9 million people in the United States have heart failure (HF), with 550,000 new patients diagnosed annually.[1] Many of these patients are characterized by a prolonged QRS duration, which indicates abnormal ventricular activation, and is a marker of both worsening cardiac function[2,3] and increased mortality.[4] Device-based treatment for HF (ie, cardiac resynchronization therapy or CRT) improves left ventricular (LV) function, oxygen uptake at peak exercise, 6-minute walk distance, quality of life scores, and change in New York Heart Association (NYHA) Class.[5–8] It has also been reported that CRT reverses the ventricular remodeling process, which has been associated with increased cardiac dimensions and decreased pumping efficiency.[9,10] A meta-analysis of 4 large randomized controlled trials indicates that CRT may also decrease mortality from progressive HF,[11] which is consistent with results reported from the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (ie, COMPANION) trial.[12]

From the [1]Carlyle Fraser Heart Center, Division of Cardiology, Emory University School of Medicine, Atlanta, Georgia; [2]Department of Medicine, University of California, San Francisco, California; [3]Department of Medicine, Duke University Medical Center, Durham, North Carolina; [4]School of Statistics, University of Minnesota, Minneapolis, Minnesota; [5]Keck School of Medicine, University of Southern California, Los Angeles, California.

Manuscript received January 21, 2004; revised manuscript received June 29, 2004; revised manuscript accepted August 23, 2004.

Reprint requests: David B. DeLurgio, MD, Carlyle Fraser Heart Center, Division of Cardiology, Emory University School of Medicine, Atlanta, GA 30365.

Supported in part by Guidant Corporation, St. Paul, Minnesota.

1071-9164/$ - see front matter

doi:10.1016/j.cardfail.2004.08.163

The first generation of CRT devices approved in the United States used simultaneous biventricular (BiV) stimulation to resynchronize the left and right ventricles. It has been proposed that pacing the left ventricle is the key to providing CRT, with or without right ventricular pacing.[13] Preliminary studies suggest that LV pacing is equivalent to BiV pacing terms of hemodynamics, ventricular reverse remodeling, and long-term clinical effect.[13–21] At least 2 studies indicate that LV pacing provides a small but statistically significant improvement over simultaneous BiV pacing in LV dP/dt.[14,15] Other reports indicate that BiV pacing may be superior to LV pacing in reducing LV end-diastolic diameter[21] and increasing peak endocardial acceleration.[22] Data from a large randomized trial are needed to evaluate the use of LV pacing for the treatment of HF.

Sequential BiV pacing has also been proposed as an alternative to simultaneous BiV pacing. Sequential BiV pacing allows decoupling of the ventricular pacing pulses to provide prestimulation of 1 ventricle, thus compensating for a conduction delay on that side. Several reports indicate that compared with simultaneous BiV pacing, sequential BiV pacing provides many patients with narrower QRS intervals,[23] increased LV function,[24,25] and increased 6-minute walk distance.[26] The Device Evaluation of CONTAK RENEWAL 2 and EASYTRAK 2: Assessment of Safety and Effectiveness in Heart Failure (DECREASE-HF) clinical investigation is the first large randomized controlled trial to compare both LV pacing and sequential BiV pacing with simultaneous BiV pacing.

Study Design and Goals

The DECREASE-HF trial is a prospective, multicenter, randomized, double-blind trial designed to determine if LV pacing and sequential BiV pacing are equivalent to simultaneous biventricular pacing after 6 months of therapy. The primary endpoint for assessing therapy equivalence combines peak oxygen consumption (VO_2) and LV end-systolic dimension (LVESD), which represent measures of functional capacity and cardiac reverse remodeling, respectively. Secondary and ancillary therapy endpoints include 6-month change in NYHA Class, quality of life (based on the Minnesota Living with Heart Failure Questionnaire), peak VO_2, LVESD, and other echocardiographic measures.

The overall safety and effectiveness of the device system will also be evaluated by assessing: (1) freedom from HF-related adverse events; (2) freedom from system-related complications; (3) freedom from LV lead-related complications; (4) ventricular fibrillation detection time; (5) ability to deliver continuous appropriate CRT pacing; and (6) electrical performance of the LV lead (pacing threshold, pacing impedance, and R-wave amplitude).

All patients will undergo an implant procedure for the CONTAK RENEWAL 2/4/4HE/EASYTRAK 2 system. Between implant and a 2-week follow-up visit, devices will be programmed to provide antitachycardia therapy, but not to deliver CRT. At the 2-week visit, patients complete baseline testing and receive a randomization assignment (LV pacing, simultaneous BiV pacing, or sequential BiV pacing) in a 1:1:1 ratio. Patients who are unable to complete baseline testing will not be given a randomization assignment, but will be followed throughout the study for safety data. These patients, along with patients who cannot be programmed according to their randomization assignment because of recommendations made by the device, are considered to be in a separate "safety arm," as shown in Fig. 1. All patients have an equal chance of being placed in the safety arm, regardless of randomization assignment. Patients in the safety arm do not undergo special testing, but are otherwise followed normally and counted toward safety endpoints.

Patient Population

To participate in the study, patients must be 18 years of age or older, have moderate or severe HF (NYHA Class III or IV) despite optimal pharmacologic therapy (OPT), QRS duration of 150 ms or greater, ejection fraction of 35% or less, and a life expectancy of longer than 6 months. Patients must not have had previous CRT or currently have indications for antibradycardia pacing. The definition of OPT includes 30 days of stable angiotensin-converting enzyme inhibitor and β-blocker therapy.[27,28] Additionally, patients must have been prescribed to a β-blocker for 90 days. All DECREASE-HF enrollment criteria are listed in Table 1.

Endpoints

The DECREASE-HF study is designed to evaluate 3 different CRT modalities for equivalence and to evaluate safety and effectiveness of the device system. The primary endpoint used to compare the treatment arms (LV pacing and sequential BiV) with the control arm (simultaneous BiV pacing)

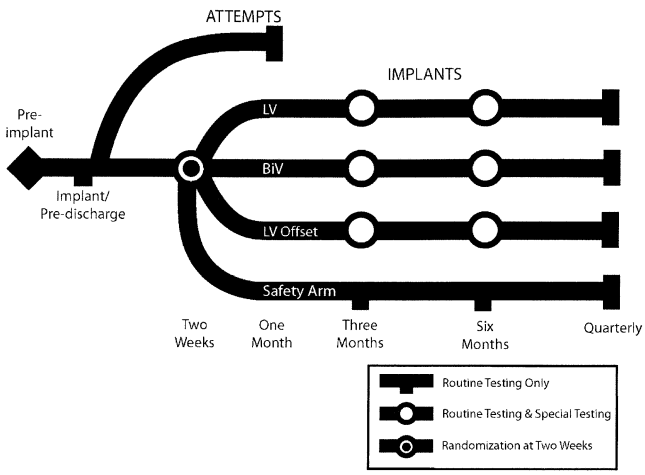

Fig. 1. Device Evaluation of CONTAK RENEWAL 2 and EASYTRAK 2: Assessment of Safety and Effectiveness in Heart Failure randomization arms and follow-up testing. BiV-CRT, simultaneous biventricular pacing; LV offset, sequential BiV pacing; LV-CRT, LV pacing.