Impact of Cardiac Resynchronization Therapy on Exercise Performance, Functional Capacity, and Quality of Life in Systolic Heart Failure With QRS Prolongation: COMPANION Trial Sub-Study

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ABSTRACT

Background: A total of 405 participants in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure trial were prospectively enrolled in an exercise sub-study designed to study the influence of cardiac resynchronization therapy (CRT) on measures of exercise capacity, functional capacity, and quality of life (QOL).

Methods and Results: Substudy eligibility included New York Heart Association (NYHA) functional Class III or IV heart failure, left ventricular ejection fraction ≤0.35, QRS interval of ≥120 ms, normal sinus rhythm, a heart failure hospitalization (or equivalent) within 1 year, a peak VO_2 ≤22 mL·kg·min, the ability to walk 150 to 425 meters in 6 minutes, forced expiratory volume in 1 second/forced vital capacity ≥50%, and no clinical indication for a pacemaker or implantable cardioverter-defibrillator. Patients were randomized in a 1:4 ratio to optimal medical therapy (OPT) or to OPT plus CRT. Cardiopulmonary exercise testing (peak VO_2 and 6-minute walk distance [6MWD]) and assessment of NYHA functional class and QOL were assessed at baseline and at 3 and 6 months of assigned therapy. There was no significant improvement in peak VO_2 at 6 months in the CRT group compared with the OPT group (+0.63 mL·kg·min) by unadjusted analysis ($P = .05$) or by analyses adjusted for missing data. Thus the primary end point of the study was not met. There was significantly greater improvement in the 6MWD in the CRT group compared with the OPT group at both 3 and 6 months by both statistical methods ($P \leq .045$). Likewise, a greater proportion of CRT patients improved by 1 or more NYHA functional classes ($P < .01$) at 3 months and had better QOL scores ($P < .01$) at 3 and 6 months compared with the OPT patients. Baseline peak VO_2 predicted clinical events (time to death, time to death or first hospitalization, or time to death and first heart failure hospitalization: $P < .05$) in CRT participants.

Conclusion: CRT patients with moderate to advanced symptoms of systolic heart failure and prolonged QRS intervals benefit from the addition of CRT to OPT in terms of exercise capacity, functional status, and QOL. CRT should be considered standard therapy in this select group of heart failure patients. (*J Cardiac Fail 2008;14:9–18*)

Key Words: Peak VO_2, 6-minute walk distance, New York Heart Association functional class.

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All decisions regarding this manuscript were made by a guest editor.

Manuscript received November 14, 2006; revised manuscript received July 27, 2007; revised manuscript accepted August 1, 2007.

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Supported by a grant from Guidant Corporation.

1071-9164/$ - see front matter

doi:10.1016/j.cardfail.2007.08.003

Heart failure is a common health problem characterized by congestive symptoms, fatigue, exercise intolerance, and short survival.[1–3] Improvements in these features of heart failure are achieved through the judicious use of optimal pharmacologic therapies (OPT).[2–4] In patients with modest to advanced symptomatic heart failure and a prolonged QRS interval resulting in coincident intraventricular dyssynchrony, the addition of cardiac resynchronization therapy (CRT) to OPT has been shown to improve direct and surrogate measures of exercise capacity,[5–11] as well as to reduce death or hospitalization from any cause[12] and death from any cause.[7] As heart failure patients begin to live longer, finding means to improve their quality of life, such as through improved exercise performance, becomes paramount and CRT may be such a means.

The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial compared OPT with OPT plus CRT alone (CRT-P) and to OPT plus CRT with an implantable cardioverter-defibrillator (ICD) (CRT-D) in heart failure patients with a QRS interval $\geq$120 ms and a left ventricular ejection fraction $\leq$0.35.[12] The primary analysis and publication of this trial showed that OPT plus CRT-P or CRT-D reduces the risk of death or hospitalization from any cause compared with OPT alone and that OPT plus CRT-D reduces death from any cause compared with OPT alone.[12] Additional analyses showed that OPT plus CRT (CRT-P and CRT-D combined) improves the 6-minute walk distance (6MWD), the quality of life (QOL) score, and the New York Heart Association (NYHA) functional class compared with OPT-alone participants. Other prospective, randomized trials of CRT versus OPT-alone in heart failure patients with prolonged QRS intervals have shown similar improvements in measures of exercise performance.[5–11] These data suggest that one benefit of CRT, when added to OPT in appropriate heart failure patients, is to improve exercise and functional capacity through resynchronization of ventricular contraction, adaptive cardiac remodeling, enhanced forward cardiac output, increased musculoskeletal perfusion and respiratory gas exchange, and reduced neurohormonal activation and muscular inflammation.

The COMPANION trial prospectively included an exercise substudy. This substudy examined the oxygen exchange at peak exercise (peak VO_2) and the 6MWD at 3 and 6 months in COMPANION participants able and willing to perform serial cardiopulmonary exercise testing. The working hypothesis of the substudy was that OPT plus CRT (CRT-D and CRT-P) would improve peak VO_2 by 1.3 mL·kg·min or greater and improve the 6MWD at 6 months of assigned therapy compared with OPT alone. At the time of COMPANION exercise substudy design, data were just beginning to emerge from other prospective, randomized trials of CRT on the impact of CRT on exercise capacity. This exercise substudy was performed to have adequate power to determine whether CRT improves the peak VO_2 and 6MWD over time and to contribute to emerging data on this issue.

Methods

COMPANION Trial

The COMPANION trial enrolled 1520 heart failure patients in 128 US medical centers.[12] Eligibility for COMPANION trial enrollment included NYHA Class III or IV heart failure, an electrocardiogram demonstrating a QRS interval of 120 milliseconds or more, a PR interval of 150 ms or more and normal sinus rhythm, a left ventricular ejection fraction of 0.35 or less, a left ventricular end-diastolic dimension of 60 mm or more (or more than 30 mm/m^2), age $\geq$18 years, the absence of a clinical reason for a pacemaker or implantable defibrillator, and a heart failure hospitalization (or equivalent) in the 12 months preceding study entry. Eligible patients were prospectively randomized in a 1:2:2 ratio to receive protocol-specified OPT, OPT plus CRT-P, or to OPT plus CRT-D. The details of OPT, CRT-P (device and placement), and CRT-D (device and placement) have previously been described.[12] The primary end point of the COMPANION trial was a composite of any cause death or any cause first hospitalization. The secondary end point was any cause death. Other protocol-specified analyses performed and published included adverse events and a longitudinal assessment of NYHA functional class, 6MWD, and QOL as measured by the Minnesota Living with Heart Failure questionnaire.[12] The COMPANION trial steering committee, end points committee, and sponsor were all blinded to participant treatment assignments. The participants, their physicians, the statisticians, and the data safety and monitoring board were not blinded.

Exercise Substudy

A protocol-specified exercise substudy was performed at 67 of the 128 US COMPANION medical centers (see Appendix). It was hypothesized that OPT plus CRT would improve exercise capacity in patients meeting COMPANION exercise substudy eligibility criteria compared with similar patients receiving OPT alone. Eligibility criteria for entry into the substudy included meeting all primary COMPANION trial entry criteria as well as peak VO_2 of $\leq$22 mL·kg·min and a 6MWD of 150 to 425 meters. Other exercise substudy entry criteria excluded any neuromuscular or vascular disease precluding normal walking, any medical contraindications to exercise testing, and a forced expiratory volume in 1 second/forced vital capacity $<$50%. In this substudy, the peak VO_2 was determined in a standardized fashion[13] at study entry and again 3 and 6 months into treatment assignment. The primary substudy end point was change (Δ) in peak VO_2[14] at 6 months of randomized therapy. Exercise substudy participants were considered evaluable for the primary end points if they had a qualifying baseline peak VO_2 and 6MWD and had either a peak VO_2 or a 6MWD performed at either 3 or 6 months of post-assignment treatment. Secondary substudy end points were Δ in 6MWD,[14] Δ in NYHA functional class, and Δ in QOL assessment (the Minnesota Living with Heart failure questionnaire)[15] at 3 and 6 months of randomized therapy.

Participants underwent exercise testing using a modified Balke treadmill protocol and continuous expired gas analysis. Resting and exercise vital signs were obtained. The exercise duration and exercise-limiting symptoms were recorded. The peak VO_2 and respiratory exchange ratio (RER) were averaged over the last 15 seconds of the exercise test. The ventilatory equivalent (VE/VCO_2 slope) was calculated from start of exercise to the end of exercise. All exercise data were electronically sent to an