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STATE-OF-THE-ART PAPER

Lessons Learned and Insights Gained in the Design, Analysis, and Outcomes of the COMPANION Trial

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ABSTRACT

COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure), the first cardiac resynchronization therapy (CRT)–heart failure mortality and morbidity controlled clinical trial planned, conducted, and reported, was a randomized, 3-arm study that compared CRT delivered by a biventricular pacemaker (CRT-P) or a CRT defibrillator device (CRT-D) with optimal pharmacological therapy alone. The patient population had advanced chronic heart failure with QRS interval prolongation ≥120 ms and reduced left ventricular ejection fraction (heart failure with reduced ejection fraction). COMPANION had a composite hospitalization and mortality endpoint as the primary outcome measure but was also powered for mortality as the first secondary endpoint. The conduct of COMPANION was challenged by important issues that arose during the trial, the most important of which was U.S. Food and Drug Administration approval of CRT devices. Along with other challenges, this issue was appropriately dealt with by the Steering Committee and the Data and Safety Monitoring Committee and did not negatively affect trial results or conclusions. We report here updated analyses from the study, which are consistent with previously published results indicating that CRT-P or CRT-D has favorable effects on heart failure morbidity and mortality in a patient population "precision" selected by the surrogate marker of increased QRS interval duration. New analyses indicate that increasing the number of classes of neurohormonal inhibitor concurrent therapy has a positive effect on CRT mortality reduction. Hypothesis-generating new findings are that in patients receiving beta-blocker therapy, the mortality reduction advantage of CRT-D versus CRT-P may be minimized or eliminated and that there may be adverse effects of CRT-D defibrillator shocks on pump failure–related outcomes. (J Am Coll Cardiol HF 2016;■:■–■) © 2016 by the American College of Cardiology Foundation.

More than a decade ago it was first reported that a medical device, a biventricular pacemaker that produced "cardiac resynchronization" (see **Central Illustration**), could dramatically improve the natural history of a subpopulation with advanced chronic heart failure with reduced left ventricular ejection fraction (HFrEF) that had been selected by means of a surrogate marker of left ventricular (LV) dyssynchrony, surface electrocardiographic QRS interval lengthening (1). Although the results of COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure) (1) and the design-related, subsequently conducted CARE-HF (Cardiac Resynchronization-Heart Failure) trial (2) have been widely reported, many of the clinical trial issues, investigational insights, and effectiveness outcomes from COMPANION have not been comprehensively described in an integrated fashion. The purpose of this report is to present and discuss some of the lessons learned and insights gained from

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ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ACH = all-cause hospitalization

ACM = all-cause mortality

ARB = angiotensin receptor blocker

CI = confidence interval

CRT = cardiac resynchronization therapy

CRT-D = cardiac resynchronization therapy with an implantable cardioverter-defibrillator

CRT-P = cardiac resynchronization therapy with only pacing capability

CVH = cardiovascular hospitalization

CVM = cardiovascular mortality

DSMC = Data and Safety Monitoring Committee

FDA = U.S. Food and Drug Administration

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

HFH = heart failure hospitalization

ICD = implantable cardioverter-defibrillator

IVCD = intraventricular conduction delay

LV = left ventricular

NHI = neurohormonal inhibitor

NNT = number needed to treat

OPT = optimal pharmacological therapy

PFD = pump failure death

SCS = sudden cardiac death

the COMPANION trial, as well as to report new analyses from the final database.

Dyssynchronous LV contraction caused by intraventricular conduction delays (IVCDs) occurs in 15% to 30% of patients with chronic HFrEF (3,4). IVCD-associated mechanical dyssynchrony reduces LV systolic function and increases risk for cardiovascular morbidity and mortality (3,4). IVCD-associated mechanical dyssynchrony can be corrected with biventricular (5-9) or LV (6,7) pacing, termed cardiac resynchronization therapy (CRT). When measured by sensitive methods, systolic function was shown to improve in all left ventricles investigated in these pioneering studies (7,9,10). Early studies measuring functional capacity (11,12), the energetic cost of improved LV chamber contractility (10), and reverse remodeling (13) suggested that CRT had the potential to reduce major clinical endpoint outcomes in HFrEF, and implantable cardioverter-defibrillators (ICDs) had been shown to reduce mortality risk in patients with ischemic cardiomyopathy and no sustained ventricular arrhythmias (14,15). On the basis of these data, the heart failure investigators involved in the planning of COMPANION recommended to the sponsor that a major heart failure clinical outcomes trial be performed, evaluating the effects of both CRT with only pacing capability (CRT-P) and CRT with an ICD (CRT-D).

The COMPANION trial, conducted at 128 U.S. centers between January 20, 2000, and November 30, 2002, was designed to evaluate whether CRT-P or CRT-D plus optimal pharmacological therapy (OPT) was beneficial compared with OPT alone in patients with advanced HFrEF with dyssynchronous LV contraction as detected by the surrogate marker of QRS interval lengthening (**Figure 1**) (1,16). Because the placement of a device may lead to adverse events requiring hospitalization, the primary endpoint was time to all-cause mortality (ACM) or all-cause hospitalization (ACH) with cause-specific hospitalizations adjudicated by the Clinical Events Committee as components of the primary endpoint.

TRIAL DESIGN, EXECUTION, AND DATA ANALYSIS: LESSONS LEARNED

TRIAL DESIGN. The COMPANION trial was a collaboration among heart failure clinicians and electrophysiologists, the former coming from a drug development tradition and the latter from a medical device tradition, the sponsor, and the U.S. Food and Drug Administration (FDA) Center for Device and Radiation Health. During trial design discussions, the investigators, the sponsor, and the FDA all agreed to aim for a higher, clinical outcomes standard of evidence for COMPANION but to also obtain short-term, more traditional device outcomes for regulatory submission, such as submaximal exercise and quality of life, measured as either secondary endpoints or "other analyses." Although studies with clinical endpoints such as mortality and hospitalization reduction are common for chronic heart failure drug trials, such studies had not been required for approval of CRT devices, for which the Center for Device and Radiation Health typically determines a device to be approvable if there is a reasonable assurance of safety and effectiveness (17).

Patients were randomized in a 2 (CRT-P) to 2 (CRT-D) to 1 (OPT) ratio (**Figure 1**). The enrollment criteria ensured an advanced (New York Heart Association class III or IV) HFrEF (LV ejection fraction ≤0.35) population, with a liberal definition of IVCD as a QRS duration ≥120 ms (1,16). OPT consisted of diuretic agents, either angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), beta-blockers, and spironolactone as tolerated. As such, COMPANION was the first heart failure clinical trial to require "triple" neurohormonal inhibitors (NHIs) as background therapy. The particular CRT-P and CRT-D devices from the sponsor (The Guidant Corporation, now Boston Scientific Corporation) have been described elsewhere (1,16). The trial had an academic-based Steering Committee, an independent Data and Safety Monitoring Committee (DSMC), and an independent Statistical Data Analysis Center.

The trial was unblinded because of ethical concerns related to implanting a nonfunctioning medical device for a substantial amount of time (median follow-up was anticipated to be at least 1 year) in the OPT arm. The primary outcome was time to the first occurrence of the composite of ACM, ACH, or its equivalent using Kaplan-Meier methodology (18,19). Two scenarios for treatment of decompensated heart failure with intravenous medications were considered to be the equivalent of heart failure hospitalization (HFH) or ACH (1). ACM was the highest order secondary outcome in the COMPANION protocol (1,16). The elective hospitalizations required for the initial implantation of the CRT-P or CRT-D were not considered endpoints. Patients with existing indications for pacemaker or defibrillator implantation were excluded from the study, as were patients with atrial fibrillation or other uncontrolled atrial