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 $\geq 120$ 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 the clinical trial was funded by Boston Scientific. Data analysis was supported by the Statistical Data Analysis Center, University of Wisconsin. Dr. Saxon and the University of Southern California receive research support from Boston Scientific (<$25,000/year). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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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-defibrillator (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 trial required “triple” neurohormonal inhibitors (NHIs) as background therapy. The particular CRT-P and CRT-D devices from the sponsor (The Guidant Corporation) have been described elsewhere (1,16). The enrollment criteria ensured an advanced (New York Heart Association class III or IV) HFrEF (LV ejection fraction $\leq 0.35$) population, with a liberal definition of IVCD as a QRS duration $\geq 120$ 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
tachyarrhythmias. If a patient received an appropriate ICD device during the trial for an electrophysiological indication, it was classified as a nonelective hospitalization and counted as an endpoint. All other device implantations post-initial implantation were classified as elective, as with the initial implantations in the CRT-P and CRT-D arms, unless they were implanted during an HFH, in which case they were considered endpoints. All analyses were based on intention-to-treat, with comparisons of time to event by the log-rank test (19). The final results were adjusted for the interim analyses conducted by the DSMC using the methods of Lan and DeMets (20) and an O’Brien-Fleming-type boundary (21).

The trial was event driven, with a target of 1,000 confirmed primary events estimated to take 3 years to accrue on the basis of randomization of 2,200 patients over 2 years and a minimum follow-up period of...

**CENTRAL ILLUSTRATION** Correction of LV Mechanical Dyssynchrony by Biventricular Pacing

**FIGURE 1** COMPANION Study Design

A 1:2:2 randomization scheme was used among optimal pharmacologic therapy (OPT), OPT plus cardiac resynchronization therapy with only pacing capability (CRT-P), and OPT plus cardiac resynchronization therapy with an implantable cardioverter-defibrillator (CRT-D), respectively. COMPANION = Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure; ICD = implantable cardioverter-defibrillator.
1 year. Sample size estimates were based on a 12-month primary endpoint rate of 40% in the OPT-alone arm and a 25% reduction in the event rate in either OPT-plus-device arm (16) (Table 1). The trial had approximately 95% power to detect a 25% reduction in the primary outcome and approximately 80% power to detect a 25% reduction in mortality alone, in either device arm versus the OPT-alone arm at a sample size of 2,200. The overall alpha level of 0.05 was not divided equally for the 2 key comparisons of the primary endpoint. Rather, an alpha level of 0.03 was set for the CRT-D versus OPT comparison and a level of 0.02 was set for the CRT-P versus OPT comparison. In addition to the primary endpoint evaluation, the statistical analysis plan described in the COMPANION protocol also allocated an overall alpha level of 0.05 to ACM as the highest order secondary endpoint, with 80% power to detect a difference between either device arm and OPT alone. The DSMC consisted of 4 clinicians plus an academic biostatistician not associated with the study conduct.

**TRIAL EXECUTION.** Lessons are learned from every trial conducted, and COMPANION as the first major clinical outcomes trial evaluating CRT and still the only trial evaluating both CRT-P and CRT-D was certainly no exception. Most of the challenges and in-trial difficulties can be attributed to attempting to perform an unblinded clinical outcomes trial evaluating a medical device whose implantation is nontrivial and can be accompanied by serious adverse events, and then market introduction of the same types of devices during the trial. The major challenges encountered in the trial are summarized in Online Table 1.

**Operational challenges.** In the early stages of COMPANION, an unacceptable complication rate of device implantation was encountered, arising from trauma related to inexperienced operators’ placing the LV lead through the coronary sinus. This was quickly appreciated by the sponsor and the DSMC and reported to the Steering Committee. Remedial measures were recommended by the Steering Committee that included additional training in the sponsor’s laboratories, increased proctoring of cases performed by first-time implanting physicians, and limitations on procedure duration. These measures were successful, and ultimately the procedure and device serious adverse event rate was ≤10% in both CRT groups and <2% for the combination of any coronary sinus dissection or perforation or cardiac tamponade (1). The alertness of the DSMC and the sponsor to early operational issues was important to the successful completion of the trial, which would have been discontinued if the serious adverse event rate had not been brought quickly down to acceptable levels.

One of the major challenges to successful completion of COMPANION was FDA approval of both CRT-P and CRT-D devices during the trial (Figure 2), in each case on the basis of relatively short-term functional endpoints. In August 2001, at an enrollment of approximately 750 patients, the FDA approved Medtronic’s InSync CRT-P device (22). The approval was based on the ability of the device to improve short-term exercise performance, alleviate symptoms, and improve quality of life. Less than 1 year later, in May 2002, the FDA approved Guidant’s CONTAK-CD CRT-D device (23) and, 7 weeks later, Medtronic’s InSync ICD CRT-D device (24) on the basis of functional data alone. The impact of these approvals was that recruitment for COMPANION was slowed in mid-2001 (Figure 2), decreasing from a peak of 100 patients/month to less than 10 patients/month by mid-2002. More important, the rate of crossover in the OPT arm to receive the approved devices increased as a result of CRT devices gaining FDA approval.

As a consequence of market availability of CRT devices and a related loss of investigator equipoise, by the end of the trial, the withdrawal rate in the OPT-alone arm had risen to 26%, compared with 6% in the CRT-P-plus-OPT arm and 7% in the CRT-D-plus-OPT arm. The differential withdrawal rates among the 3 arms led to a shorter period of follow-up in the OPT group (11.9 months vs. 16.2 and 15.7 months in the CRT-P and CRT-D arms, respectively) (1). Although the baseline characteristics between those who remained and those who dropped out were similar (1), the potential for bias in clinical outcomes remained. In addition, the loss of patients from the OPT-alone arm, which by design had only one-fifth of patients randomized, resulted in a loss of power to detect an intervention effect. Increasing the impact of the differential withdrawal rate was that patients who dropped out of the OPT-alone arm did so by withdrawing consent, with most of them in effect crossing

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**Table 1** COMPANION: Pre-Trial Sample Size Assumptions Versus Observed Trial Results

<table>
<thead>
<tr>
<th>Event Rates, Annualized</th>
<th>Effect Size, t</th>
<th>Sample Size</th>
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<tr>
<td>Event Rates, Annualized</td>
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<td>Power</td>
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<tr>
<td>Pre-trial assumptions</td>
<td>40% IEP</td>
<td>25%</td>
<td>2,200</td>
</tr>
<tr>
<td>Observed results</td>
<td>67.5% IEP</td>
<td>18% CRT-P</td>
<td>1,520</td>
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*Time-to-event estimates or observed data at 12 months. †Effect sizes as percentages, (1 hazard ratio) > 100. ACM = all-cause mortality; COMPANION = Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure; CRT-D = cardiac resynchronization therapy with an implantable cardioverter-defibrillator; CRT-P = cardiac resynchronization therapy with only pacing capability; IEP = primary endpoint; 2EP = secondary endpoint.*
over and receiving CRT devices. Once the crossover rate began to escalate, the Steering Committee, sponsor, and FDA agreed to attempt to stem this practice by assigning a class I deviation to the responsible investigator, which carries substantial regulatory implications. This “enforcement” policy was unsuccessful and instead increased incentive to withdraw consent for the study prior to crossover. In such patients, the primary outcome could not be attained for subsequent follow-up. The COMPANION Steering Committee quickly recognized this dilemma and developed a plan to approach the patients who withdrew to obtain reconsent for basic follow-up for survival and hospitalization status. As a result, 128 patients (155 withdrawals minus 26 patients withdrawn for heart transplantation and 1 for emergency medical care) had to have their endpoint status reviewed, and then 68 patients were recontacted to determine their primary outcomes and vital status. Because this required local Institutional Review Board approval, a delay of several months occurred before the results of COMPANION could be finalized. After completion of this process, the primary outcome status was obtained in 91% of the OPT arm and 99% of the each of the 2 device arms. For mortality, vital status was obtained for 96% of the OPT arm and 99% of the device arms. To rule out that there was any substantial bias, various sensitivity analyses were conducted that included best case (all withdrawn patients whose outcomes were unknown were assumed to be free of primary endpoints prior to the November 30, 2002, end of the trial), worst case (all unknown-status patients were assumed to have had endpoints prior to November 30, 2002), and all patients censored at the time of withdrawal. None of these analyses altered the outcome of the primary endpoint.

The lesson here is that consent forms can be constructed prospectively to deal with various levels of withdrawal, obviating the need to reconsent. A 3-part document can and should be structured for different levels of withdrawal (i.e., from the intervention only but continuing in the trial for full follow-up, from the intervention and study visits but allowing subsequent patient or family contact for determination of vital status or other important clinical events, and complete withdrawal with no further contact by study personnel). This type of multitier consent process is currently in use in drug and pharmacogenetic trials and is consistent with the ethics of obtaining all possible useful information from research subjects who have agreed to participate in a trial designed to discover new and important information relevant to the disease afflicting themselves and other enrolled patients (25).

The slowing of enrollment in mid-2001 meant that the duration of the trial would be lengthened, as the event-driven design meant that follow-up could be extended to compensate for the slower accrual. However, such an adjustment cannot compensate for increased dropout and crossovers. Fortunately, the control arm (OPT) event rate and to a lesser extent the CRT arms’ effect sizes were able to compensate for the dropout and crossover problems. Key to addressing the concern over bias related to a differential dropout rate was the robustness of the primary outcome and its components. All-cause death is not subject to bias as long as follow-up is complete. However, hospitalizations may be triggered for different reasons in open, unblinded trials, and thus bias could be introduced in combined endpoints. Some contemporaneous CRT device trial designs have been able to capitalize on an ICD indication in patients with heart failure and implant CRT-D devices with the CRT function off in an effectively blinded control group (26). However, when COMPANION was planned and conducted, ICDs were not approved for chronic heart failure populations, obviating this option. Ultimately, a mortality endpoint, relatively free of any investigator or data input bias, and careful adjudication of hospitalization events by a clinical events committee are the best antidotes to potential bias in an unblinded trial.

**Trial completion.** In mid-November 2002, a DSMC review observed 941 primary events, nearing the target of 1,000 events, and notified the Steering
Committee that the trial should close enrollment and plan to terminate follow-up sometime in the next few weeks. On the basis of this information, the Steering Committee elected to stop enrollment on November 18, 2002, with a sample size of 1,520 patients, and to terminate follow-up on November 30, 2002 (i.e., with no primary events occurring beyond November 30 counted in the data analysis). Through that date, 1,020 primary events were ultimately identified. Thus, the duration of enrollment was 2.83 years compared with the estimated 2.0 years, the total duration of the trial was 2.86 years compared with the predicted 3.0 years, and minimum follow-up was 12 days compared with the expected 1 year.

**DATA ANALYSIS.** The statistical analysis plan developed prior to the end of the trial by the Steering Committee in consultation with the Statistical Data Analysis Center needed to take into consideration the disproportional withdrawal. On the basis of policy formulated by the Steering Committee, the statistical analysis censored patients who had been withdrawn for elective CRT device implantation at the time of the elective hospital entry, but if they were reconsented, vital status and hospitalization data were collected and used after their initial withdrawal, with the elective hospitalization for device implantation not counting as a primary endpoint. If the patient could not be reconsented or if follow-up data were otherwise indeterminate, the patient was censored at withdrawal. Of the 155 withdrawals, 87 had previous primary endpoints, and 47 of the 68 who had no previous endpoints were reconsented with ascertaining of the primary endpoint. The intention-to-treat handling of events and the large treatment effects in the CRT arms meant that patients who received CRT-P or CRT-D devices without having primary endpoints were true crossovers to device therapy, and this in effect lowered the event rates in the OPT group. There were 44 such patients in the OPT group, 15 in the CRT-P group, and 9 in the CRT-D group. Thus, the relative treatment effects in both CRT arms was somewhat underestimated by crossover to device therapy, which occurred in 14% of the OPT patients.

**UPDATED RESULTS, NEW ANALYSES, AND INSIGHTS GAINED**

**RESULTS.** Updated final database. The COMPANION database has undergone 3 updates since the original analyses for the submission of the primary report (1) in September 2003, in April 2004 in preparation for a regulatory submission (previous “final” database and study report), and in November 2015 to accommodate additional updates on endpoint entry errors that had been detected during the intervening period. We consider the November 2015 database and the accompanying study report to be final (“updated final database”), which is and will be used in this and subsequent reports. The differences between the updated final database and the pre-final database used for the original publication (1) are given in Online Table 2. None of the changes are substantive, and results and statistical findings do not differ between the analyses.

**Study population.** The final trial population baseline characteristics are given in Online Table 3. In line with the inclusion criteria, the COMPANION study population was unambiguously advanced, high-risk HFrEF, all New York Heart Association class III or IV (with 14% class IV), age 67 years, 55% ischemic heart disease, and an average 6-min walk distance of 262 m. Pharmacologic therapy was likely close to optimal for what can be delivered to such a HFrEF IVCD population, with 89% of subjects on ACE inhibitors or ARBs, 68% on beta-blockers, and 55% on spironolactone. On the basis of clinic visit medication records, 61% of subjects were actually receiving ACE inhibitors or ARBs plus beta-blockers, and 34% were receiving ACE inhibitors or ARBs, beta-blockers, and spironolactone (Online Table 3).

**Predicted versus actual results.** As presented in Table 1, there was reasonable agreement between pretrial assumptions and observed results, with the OPT-alone group having a primary endpoint event rate higher than expected (observed 67.5% vs. predicted 40%). The secondary (ACM) endpoint was slightly less than expected (18.5% vs. 24% from time-to-event analysis at 12 months) but was 25% when entire trial event rates were normalized to 12-month follow-up. Effect sizes for the primary endpoint were somewhat less than predicted in both device arms (18% to 19% observed vs. 25% predicted) but were greater than expected for ACM in the CRT-D arm (36% vs. 25% predicted). As a result of the higher than expected control arm (OPT alone) event rate, the absolute reduction in the primary endpoint rate was approximately 11.5% (from 67.5% to ~56%) (Online Table 4) in both device arms compared with the predicted absolute event rate reduction of 40% to 30%, or by 10%. In terms of statistical power, for the primary endpoint, slightly lower than expected effect sizes were balanced by a higher than expected control arm event rate, leading to a slightly higher than expected absolute event rate reduction in both device arms. For the ACM secondary endpoint, a slightly lower than expected OPT arm 12-month event rate was overcome by a higher than expected effect size in the CRT-D arm.
CRT-P (Plus OPT) or CRT-D (Plus OPT) versus OPT alone. Figure 3A presents the time-to-event analysis for the primary event of ACM or ACH with a total of 1,020 primary events (64 [6.3%] ACM, 935 [91.7%] ACH, and 21 [2.1%] hospitalization equivalent). Figure 3B presents the time-to-ACM analysis. Both the primary endpoint (p = 0.014) and mortality (p = 0.003) were significant for the CRT-D versus OPT comparisons, crossing the pre-specified boundaries. The primary outcome (p = 0.016) was significant for the CRT-P versus OPT comparison, with mortality having a nonsignificant (p = 0.059) beneficial trend.

Figure 3 gives time to ACM or cardiovascular hospitalization (CVH) (Figure 3C) and to ACM or HFH (Figure 3D), data similar to those previously published (1). Hazard ratios for these endpoints as well as for additional clinical endpoints are given in Online Table 3. As expected, for CRT-P, there is a progressive decrease in the hazard ratio as the combined endpoints become more cardiac and heart failure specific, ranging from 0.82 to 0.66 to 0.64 going from ACM or ACH to ACM or HFH to cardiovascular mortality (CVM) or HFH, respectively. This supports the mechanism of action of CRT as being specific to the failing heart.

The hazard ratios for various endpoints given in Online Table 4 and the cognate effect sizes in Online Table 5, on a background of the most effective pharmacological therapy, indicate very large and meaningful treatment effects that are comparable with or exceed the largest effect sizes observed in placebo-controlled pharmacological therapy HFrEF trials, most of which were generated on backgrounds of fewer effective drug classes (27-33) (Online Table 5).
NEW ANALYSES. Effects of CRT-P or CRT-D in patients receiving multiple NHIs. Figure 4 gives time-to-event curves for the primary endpoint or ACM in the 61% of patients who were actually receiving ACE inhibitors or ARBs plus beta-blockers (“double neurohormonal inhibition”), during the trial. Both CRT-P and CRT-D were highly effective in the presence of these mainstay HFpEF pharmacological classes, with hazard ratios that were numerically lower (Online Table 4) and effect sizes that were higher (Online Table 5) than in the entire cohort. With the 34% subpopulation that received “triple neurohormonal inhibition” therapy, consisting of the addition of spironolactone to an ACE inhibitor or ARB plus a beta-blocker, hazard ratios for mortality endpoints and CVM or CVH are even lower, with CRT-D associated with a 56% reduction in ACM. That is, CRT therapy may be more effective on a background of maximal neurohormonal inhibition than in the absence of such therapy. The most general explanation for this is that CRT is operating through a mechanism separate from that of NHIs, and its effects are therefore additive. Possible specific additive-synergistic interactions include the positive inotropic effect of CRT, compensating for any myocardial function depressive effects of beta-blockers, and NHIs, especially beta-blockers, promoting a higher percentage of CRT pacing, by slowing sinus rates and delaying native atrioventricular conduction times, by preventing atrial fibrillation, or by reducing the triggers for premature ventricular contractions. In this regard, a higher percentage of CRT pacing, >98.5%, has been shown to be associated with greater mortality reduction, and the most common reason for lower pacing percentage was atrial fibrillation (34). An alternative explanation for these salutary CRT effects in patients on double or triple neurohormonal inhibition is that patients who can tolerate beta-blockers and/or spironolactone represent a more inherently CRT-responsive subpopulation.
CRT-P versus CRT-D. COMPANION is the only clinical outcomes trial that has compared both CRT-P and CRT-D with pharmacological therapy alone and as a result provides an opportunity to compare results between the 2 CRT devices. Figure 3B illustrates the larger ACM reduction compared with OPT by CRT-D (by 36%, \( p = 0.003 \)) versus CRT-P (by 24%, \( p = \text{NS} \)). The comparison of ACM outcomes in the CRT-D arm (105 events in 595 patients, 12.1% at 12 months) (Online Table 4) and the CRT-P arm (131 events in 617 patients, 14.7% at 12 months) yielded a hazard ratio of 0.84 (95% confidence interval [CI]: 0.65 to 1.09; \( p = 0.19 \)) (Online Table 4). CVM between CRT-P and CRT-D did achieve statistical significance (hazard ratio: 0.73; 95% CI: 0.55 to 0.98). The mortality difference between the CRT-D and CRT-P arms in Figure 3B is due entirely to a reduction in sudden cardiac death (SCD) in the CRT-D group that did not occur with CRT-P (35) (12-month event rates [Online Table 4]: SCD, OPT 5.1%, CRT-P 6.1%, CRT-D 1.7%; pump failure death [PFD], OPT 9.9%, CRT-P 5.7%, CRT-D 6.5%). The CRT-D/CRT-P hazard ratio for SCD was 0.37 (95% CI: 0.21 to 0.65), a statistically significant 63% reduction in favor of CRT-D, with no significant difference in PFD. As shown in Figures 3A, 3C, and 4D as well as in Online Table 4, when the more numerous hospitalizations of various types are included in combined endpoints with ACM or CVM, there is no advantage of CRT-D over CRT-P.  

On the basis of 12-month event rates, the number needed to treat (NNT) by CRT-D to prevent 1 cardiovascular death is 15 compared with the OPT alone group and 28 compared with CRT-P (Online Table 2). For SCD, the NNT is 29 for CRT-D versus OPT alone.
and 23 for CRT-D versus CRT-P. For PFD, the NNT for CRT-D versus the OPT-alone group is not smaller compared with that for CRT-P versus OPT, 29 and 24, respectively (Online Table 4), and neither hazard ratio is significant compared with OPT. Therefore, the advantage of CRT-D is in the prevention of SCD, which extends to CVM reduction. The much lower NNTs for hospitalization combined endpoints in Online Table 4, based on much higher event rates, do not differ between the CRT-P or CRT-D versus OPT arm. Importantly, on the strength of their reductions in hospitalizations and mortality, an extensive cost-effectiveness study indicated that both the CRT-P and the 50% more expensive CRT-D device are both within acceptable standards (36).

An inspection of the survival effects of CRT-P and CRT-D on a background of double neurohormonal inhibition therapy (Online Tables 4 and 5) yields an interesting observation. The ACM hazard ratio difference for CRT-D/OPT compared with CRT-P/OPT (Figure 3B) disappears in the 61% of COMPANION patients receiving double neurohormonal inhibition therapy (respective ACM effect sizes of 43% and 44% [Online Table 5], both hazard ratios significant vs. OPT [Online Table 4]). The same phenomenon is observed for CVM (Online Tables 4 and 5), although neither CRT-D nor CRT-P is statistically significant compared with OPT. The loss of a differential effect on mortality by CRT-D versus CRT-P is not due to the disappearance of a protective effect against SCD in the double neurohormonal inhibition cohort but rather to a higher PFD hazard ratio in CRT-D (Online Table 4). In the 34% of patients who were on triple neurohormonal inhibition therapy, both CRT-P and CRT-D reduced mortality as in the double neurohormonal inhibition patients, by the very substantial amounts of 51% and 56%, respectively. An increase in the PFD hazard ratio in the CRT-D arm versus CRT-P is
not as apparent as in the double neurohormonal inhibition subgroup, but CRT-P significantly reduced PFD (by 63%) (Online Table 4) whereas CRT-D did not (nonsignificant 50% decrease).

Could the loss of any benefit on PFD in the CRT-D group in double and possibly triple neurohormonal inhibition patients be due to the adverse effects of defibrillator shocks? It is reasonable to ask this question because ICD shocks may produce myocardial damage (37) and can be associated with increased mortality (38). In COMPANION, the incidence of ICD shocks in the CRT-D arm was a nontrivial 24%, with 61% of them appropriate for sensed ventricular tachycardia or ventricular fibrillation (39). On post hoc analysis, the appropriate shocks were associated with an increased incidence of the primary endpoint ACM and PFD (39). This is consistent with a separate analysis performed in a large cohort of more than 1,500 CRT-D-treated patients monitored daily from home, which reported that only appropriate shocks for sustained ventricular arrhythmias or atrial fibrillation or flutter predicted subsequent ACM compared with inappropriate shocks for noise, sinus tachycardia, or non-atrial fibrillation or flutter supraventricular tachycardia (38). This suggests that it is the underlying rhythm rather than the shock per se that is associated with increased event rates, and perhaps many of these patients ultimately die of pump failure, resulting in no net mortality reduction from prevention of SCD.

Against an adverse effect of defibrillator shocks arm on pump failure outcomes in the CRT-D arm is that, unlike in the double and triple neurohormonal inhibition groups, an attenuation of the reduction in PFD in the CRT-D arm was not observed in the entire cohort (PFD hazard ratios vs. OPT: 0.70 for CRT-P and 0.72 for CRT-D) (Online Table 4). However, in support of an adverse effect of ICD shocks is the cardiac transplantation rate in the 2 CRT groups, which was 2.5-fold higher with CRT-D (n = 15 [2.5%]) versus
CRT-P (n = 6 [1.0%]) (p = 0.039) but not different from OPT (n = 5 [1.6%]) (p = 0.38). These hypothesis-generating data raise the possibility that a CRT-P device is just as effective as CRT-D for mortality reduction in the presence of maximal neurohormonal inhibition therapy. However, these data should also be interpreted in light of very significant changes in ICD programming since COMPANION was published, which have greatly reduced the incidence of inappropriate shocks and shocks for nonsustained ventricular tachycardia, and in the context of CRT pacing programming advances that can help promote CRT pacing in the presence of native conduction or premature ventricular contractions. Nonetheless, if the noninferiority of CRT-P to CRT-D for mortality reduction were confirmed by a prospective comparative effectiveness trial on a background of double or triple neurohormonal inhibition therapy, CRT-eligible patients could be spared the discomfort and potential myocardial damaging effects of ICD shocks. In the absence of such a prospective trial, the standard for CRT therapy in advanced HFrEF should continue to be a CRT-D device.

**COMPANION versus CARE-HF.** Although in patients with HFrEF, COMPANION did not demonstrate a statistically significant mortality reduction advantage of CRT-P compared with OPT, subsequently the CARE-HF trial (2) did (hazard ratio: 0.64; 95% CI: 0.48 to 0.85; p < 0.002). For the primary endpoint of ACM or CVH, CARE-HF reported a hazard ratio of 0.63 (95% CI: 0.51 to 0.77) compared with 0.76 (95% CI: 0.63 to 0.90) in COMPANION for the same endpoint (Online Table 4, Figure 3). CARE-HF was conducted in Europe prior to the approval of CRT devices in that jurisdiction and did not face the same dropout and crossover issues as COMPANION and as a result had better “adherence of patients and investigators to the protocol [allowing for] the increasing effect of cardiac resynchronization over a long follow-up period.” Indeed, the mean follow-up in CARE-HF was 29.4 months (2), 2 to 3 times longer than in COMPANION (1).

The patient population of CARE-HF differed from COMPANION’s in having fewer patients in New York Heart Association class IV (6% [2] vs. 15% in COMPANION) (Online Table 3), a higher LV ejection fraction (25% [2] vs. 21%) (Online Table 3), and a much lower percentage of patients with ischemic etiology (38% [2] vs. 56% in COMPANION) (Online Table 3). Other baseline characteristics, including the intensity of pharmacological therapy, age, and IVCD characteristics were similar between the 2 trials (2) (Online Table 3). The lower mortality rate in the pharmacological therapy arm of CARE-HF (12.6% at 1 year and 12.1% annualized for the entire trial [2] vs. respective values of 18.5% and 25% for COMPANION) (Table 1 and Online Table 4) reflects a population with less advanced heart failure, better LV function, and lower ischemic heart disease compared with that of COMPANION. This is further supported by comparison of the annualized rates of the CARE-HF pharmacological therapy primary endpoint, ACM or CVH. Online Table 4 indicates that the ACM or CVH 12-month event rate in the COMPANION OPT-alone group was 59.6%; the annualized OPT event rate for the entire trial was 61.9%, compared with 22.6% in CARE-HF (2). Because of the higher event rates in COMPANION, the absolute reduction in event rates in the CRT-P arm was greater than in CARE-HF (e.g., for ACM or CVH, from 61.9% to 40.7%, by 21.2% vs. 6.7% in CARE-HF) (2). This resulted in smaller NNTs in COMPANION, for example, for ACM or CVH, an NNT of 7 (Online Table 4) versus 15 in CARE-HF. Thus, CARE-HF, conducted in a less advanced HFrEF population over a longer period of time, yielded larger effect sizes but smaller absolute event rate reductions than in the COMPANION CRT-P arm. These differences are what might be expected in the 2 patient populations, and taken together, they support CRT-P as a highly effective therapy in HFrEF, in both less advanced and very advanced class III or IV heart failure.

In CARE-HF, 19 of the 404 patients in the OPT group received activated CRT devices prior to having a primary endpoint, for a crossover rate of 4.7% compared with 14% in COMPANION. The result of this was likely that the underestimation of CRT treatment effects was less in CARE-HF than in COMPANION.

**INSIGHTS GAINED. Heart failure trial implications.** As indicated in Table 1 and Online Table 1 and the associated discussion, the COMPANION trial was successful despite formidable operational and design challenges. In addition to the substantial effectiveness of the devices being tested, a major reason for COMPANION’s success was the very high event rate for the primary and other composite mortality and hospitalization endpoints. In the neurohormonal inhibition era, an event rate for ACM or hospitalization as high as COMPANION’s, 67.5% at 12 months in the OPT-alone group, is somewhat remarkable and indicates that the protocol was able to identify an advanced HFrEF population at high risk for morbidity and mortality and that the investigators adhered to the protocol. Elements of the protocol that ensured a high control group event rate included the requirement of HFH or its equivalent in the previous 12 months (16), known to be a risk for subsequent morbidity and mortality, including rehospitalization (40,41), and of course the inclusion criterion of an IVCD (3,4).
Another important contemporary implication of the COMPANION and CARE-HF trials (2) is the successful selection of an HFrEF subpopulation expected to be more responsive to the tested intervention. This is an example of subpopulation enrichment using “precision selection” into a clinical trial, a form of personalized or precision medicine. Rather than recruiting all patients who qualify on the basis of LV ejection fraction and symptom criteria, as virtually all other HFrEF trials have done, COMPANION (1,16) as well as CARE-HF (2) and most other CRT trials required the additional inclusion criterion of an IVCD detected by a prolonged QRS interval. This is a biomarker or surrogate marker for LV mechanical dyssynchrony, the abnormality CRT is designed to correct. As recent trials with narrow or normal QRS intervals have emphasized (42,43), CRT is ineffective in the absence of QRS lengthening. In other words, if COMPANION had been conducted in a generalized HFrEF population without the lengthened QRS inclusion criterion, it almost certainly would have produced negative results. Enrichment of clinical trial populations through the use of biomarkers that identify responsive subpopulations is something that is highly desirable but difficult to attain (44), and COMPANION and CARE-HF demonstrate that this approach can be successful.

Therapeutic mechanistic insights. As originally demonstrated by Kass’s group (9), biventricular pacing in an electrically and mechanically dyssynchronous left ventricle improves systolic function (dP/dT) at no energetic cost and effectively increases the efficiency of contraction. Evidence for improved systolic function in COMPANION derived from a statistically significant increase in systolic blood pressure in the device arms compared with the OPT-alone arm (1); in patients with HFrEF with lower (<120 mm Hg) systolic pressures, such an increase is a surrogate for improved LV systolic function. In effect, in patients with HFrEF who have dyssynchronous contraction due to IVCDs, CRT is a positive inotrope, differing from pharmacological inotropes only by energetic cost, which tends to be increased in drug therapy.

Along with beta-blockers (45), CRT is 1 of 2 medical therapies for HFrEF that produces “reverse remodeling,” or decreases in LV volumes, an increase in ejection fraction, and regression of LV mass (13,46,47). This is time-dependent true biologic improvement in the failing or eccentrically hypertrophied left ventricle (45,47), accompanied by favorable effects on myocardial gene expression (48,49), and therefore it is unsurprising that CRT has major beneficial effects on HFrEF natural history. Thus, clinical outcome results from COMPANION as well as from CARE-HF (2) support the idea that a positive inotropic intervention devoid of energetic cost and proarrhythmic properties can effect reverse remodeling and substantially improve clinical outcomes in HFrEF.

Future directions. Somewhat surprisingly, efforts to replace the mechanical dyssynchrony surrogate marker of QRS lengthening with more direct measures by Doppler echocardiography or other methods have been unsuccessful (42,43). As imaging technology evolves, these attempts will and should continue.

The primary limitation of the LV pacing leads used in COMPANION was the inability to cannulate a candidate coronary sinus branch vein that provided a stable lead position and pacing threshold without phrenic nerve stimulation. These issues have been largely overcome by newer generation leads and implantation tools. Multipolar LV leads, approved by the FDA in 2011, extend the success rates of implants and offer the promise of pacing over more branch vein territory, potentially providing a greater resynchronization response (50). Endocardial LV pacing, which may offer earlier and more efficient LV activation with CRT, is still investigational (51).

CONCLUSIONS

The results of the COMPANION trial were published, and the sponsor received FDA approval for not only the intermediate functional outcomes (23) but also the primary outcome, mortality plus hospitalization for any cause, and for mortality (52). This “COMPANION indication” is for patients with HFrEF who meet COMPANION inclusion criteria and remain symptomatic despite stable “optimal” heart failure therapy (53). Currently optimal therapy may need to be revised to include ivabradine for persistently higher heart rates on a beta-blocker or sacubitril-valsartan instead of an ACE inhibitor, but neither should compromise the effectiveness of CRT.

Every trial, including COMPANION, provides a methodology learning experience as well as insights into the intervention and the condition being treated. Circumstances change with time, even during the course of a trial, and often require adaptive adjustments. Some of those changes can challenge the design and conduct of a trial, and to the extent that these challenges can be anticipated, the trial will have a better chance of success. For COMPANION, the biggest challenge was the market introduction during the trial of the devices being tested and a related progressive loss of investigator equipoise. This dilemma could not have been prevented by
conventional means, because the first device introduced was developed and marketed by a competitor. Possible solutions for this dilemma in future trials include competing sponsors’ cooperating in “multiple-arm” trials (54,55) deploying devices from each sponsor that would share a control group, and regulatory solutions such as the FDA’s delaying approval on the basis of surrogate markers if a clinical endpoint-driven phase 3 trial with the same or a comparable device is under way. The FDA is working to address some of these important issues by engaging patients in device clinical trial design and conduct (53), which may also serve to limit procedural risks and patient crossovers and withdrawals.

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APPENDIX For supplemental tables, please see the online version of this article.