Cardiac Resynchronization Therapy Reduces the Risk of Hospitalizations in Patients With Advanced Heart Failure
Results From the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) Trial

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Background—In the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial, 1520 patients with advanced heart failure were assigned in a 1:2:2 ratio to optimal pharmacological therapy or optimal pharmacological therapy plus cardiac resynchronization therapy (CRT-P) or CRT with defibrillator (CRT-D). Use of CRT-P and CRT-D was associated with a significant reduction in combined risk of death or all-cause hospitalizations. Because mortality also was significantly reduced (optimal pharmacological therapy versus CRT-D only), an assessment of the true reduction in hospitalization rates must consider the competing risk of death and varying follow-up times.

Methods and Results—To overcome the challenges of comparing treatment groups, we used a nonparametric test of right-censored recurrent events that accounts for multiple hospital admissions, differential follow-up time between treatment groups, and death as a competing risk. An end-point committee adjudicated and classified all hospitalizations. Compared with optimal pharmacological therapy, CRT-P and CRT-D were associated with a 21% and 25% reduction in all-cause, 34% and 37% reduction in cardiac, and 44% and 41% reduction in heart failure hospital admissions per patient-year of follow-up, respectively. Similar reductions were seen in hospitalization days per patient-year. The reduction in hospitalization rate for heart failure in the CRT groups appeared within days of randomization and remained sustained. Noncardiac hospitalization rates were not different between groups.

Conclusion—Use of CRT with or without a defibrillator in advanced heart failure patients was associated with marked reductions in all-cause, cardiac, and heart failure hospitalization rates in an analysis that accounted for the competing risk of mortality and unequal follow-up time. (Circulation. 2009;119:969-977.)

Key Words: cardiac resynchronization therapy ▪ defibrillators, implantable ▪ heart failure ▪ hospitalizations ▪ prognosis ▪

Despite considerable improvements in the pharmacological management of patients with heart failure (HF), the prognosis of such patients remains very poor, with reduced survival, high rates of hospitalizations, and high costs to the healthcare system.1 The Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial showed that cardiac resynchronization therapy (CRT) alone (CRT-P) or in combination with a defibrillator (CRT-D) reduced the composite end point of death and all-cause hospitalizations in patients with advanced HF.2 Similarly, the Cardiac Resynchronization–Heart Failure (CARE-HF) trial demonstrated that CRT alone reduced the composite end point of death or unplanned hospitalization from a major cardiovascular event.3 Because mortality also was significantly reduced in both studies (optimal pharmacological therapy [OPT] versus CRT-D only in the COMPANION trial), an assessment of the true reduction in hospitalization rates must consider the competing risk of death and varying follow-up time.
follow-up times. In this study, we report a nonparametric analysis of the COMPANION trial that compares the rates of hospitalizations between treatment groups in an unbiased manner by taking into consideration mortality as a competing risk and differential follow-up times.

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Methods

Study Design and Patients
The study design and the results of the COMPANION trial have been published. Briefly, COMPANION was a randomized trial that tested the hypothesis that CRT-D or CRT-P would reduce the risk of death or hospitalizations in patients with advanced HF and prolonged intraventricular conduction. A total of 1520 patients in New York Heart Association (NYHA) class III or IV with ischemic or dilated cardiomyopathy and QRS duration >120 ms were randomly assigned in a 1:2:2 ratio to OPT, CRT-P, or CRT-D. The primary end point of the study was the composite of death and all-cause hospitalization; the secondary end point was all-cause mortality. An independent end-point committee comprising 7 HF specialists adjudicated these end points. The analysis of mode of death has been published previously. This report describes the analysis of the hospitalization rates.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

Hospitalization End-Point Definitions
In COMPANION, hospitalization events were defined as an admission to a hospital for any reason that was associated with a date change or the outpatient use of intravenous inotrope and/or vasoactive drugs for HF and for a duration >4 hours. Hospitalizations for the initial implantation or for an elective implantation of a device were excluded. All hospitalizations were adjudicated and classified into either cardiac or noncardiac. Cardiac hospitalizations were further categorized into HF, myocardial infarction, unstable angina pectoris, syncope, cardiac procedure, arrhythmia based, heart transplantation, complication of cardiac medication or procedure, and other causes. Noncardiac causes included pulmonary, vascular, gastrointestinal, and renal causes, as well as noncardiac chest pain, cancer, hypovolemia, complications from noncardiac medication, and other nonspecific reasons.

Statistical Analyses
All analyses were performed in accordance with the intention-to-treat principle. Differences in baseline demographic variables and hospitalization frequency groups were analyzed with ANOVA for continuous variables and the χ² test for categorical variables. P values are all 2 sided and were considered to be statistically significant at P≤0.05. SAS software version 9.1 (SAS Institute, Inc, Cary, NC) was used for all analyses except when noted.

Crossover, Differential Withdrawal, and Follow-Up Rates Between Treatment Groups
Seventy-eight OPT patients (25%) crossed over to receive CRT during the study. Per study protocol, OPT patients who had an antecedent hospitalization for worsening of HF during follow-up could have a device implanted. These hospitalizations were included in the analysis because they were nonelective. The hospitalizations for device implantation in OPT patients who did not have an antecedent HF hospitalization were considered elective and were not included in the analysis.

Of the 78 OPT crossover patients, 21 patients (27%) had an elective CRT implant hospitalization. These 21 elective implant hospitalizations were not included in the analysis; however, all other hospitalizations for these patients were included. All hospitalizations for the remaining 57 patients who crossed over were included in the analysis. The nonelective implant hospitalizations for these patients were classified as either an implant-related hospitalization (33 of 57) or other (24 of 57) as shown in Figure 1. Because these 24 patients classified as other received a CRT device during a hospitalization for other reasons, the hospitalizations were not classified as implant related, as defined in the protocol, but were included in the analyses. All patients in the OPT group who received a nonelective CRT device were followed up in the intention-to-treat OPT arm.

A significant difference was found in the rate of withdrawal from the study between treatment groups. This information was previously reported. In the OPT group, 80 of 308 (26%) of the patients withdrew consent compared with 36 of 617 (6%) in the CRT-P group and 39 of 595 (7%) in the CRT-D group. Median duration of follow-up for death or hospitalizations in all patients was 11.9 months in the OPT group, 16.2 in the CRT-P group, and 15.7 in the CRT-D group, respectively (P<0.01, Kruskal-Wallis). This inequity of follow-up time between the treatment groups was taken into consideration in comparisons of hospitalization rates between groups.

Hospitalization Rates
The average number of hospital admissions per patient-year of follow-up, average number of hospitalization days per patient-year of follow-up, and average length of stay (days) per hospital admission are reported separately for all-cause, cardiac, HF, and noncardiac hospitalizations (Table 1 and Figure 2). These rates were calculated by dividing the total number of hospital admissions (or hospitalization days) in a treatment group by the total follow-up duration of all patients in that group. The average length of stay was calculated by dividing the total number of hospitalizations by the total number of hospital admissions. Histograms of all-cause, cardiac, and HF hospital admissions per patient-year are based on the individual rate per patient.

Comparison of Hospitalization Rates
Because comparison of hospitalization rates between treatment groups can be confounded by the competing risk of death and varying follow-up time, the Ghosh and Lin nonparametric analysis was used. This method takes into consideration mortality as a competing risk while also adjusting for follow-up time and multiple

Figure 1. Flowchart of OPT patients and crossover status. The contribution of hospitalization data from OPT patients who crossed over and received a device is shown.

OPT

No Crossover

Crossover to Device

Included

57 Hospital Admissions
for Non-elective Implant**

Not Included

21 Hospital Admissions
for Elective Implant

*Each patient has a single hospital admission associated with the implant of the device. Implant-related hospitalizations were included in the analysis if there was an antecedent heart failure hospitalization.

**Of the 57 hospitalizations associated with a device implant, 33 were implanted during the initial heart failure hospitalization. Nine were IV inotropes or vasodilative drugs, four were IV diuretics, four were positive electrophysiology studies, and seven were other non-implant-related.
Table 1. Hospital Admission Rates

<table>
<thead>
<tr>
<th>Type of Hospital Admissions and Randomized Group</th>
<th>n</th>
<th>Percentage of Total</th>
<th>Average Admissions per Patient-Year of Follow-Up, n</th>
<th>Average Hospitalization Time, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT-D</td>
<td>919</td>
<td>...</td>
<td>1.20</td>
<td>6630 8.6 7.2 372 (63)</td>
</tr>
<tr>
<td>CRT-P</td>
<td>993</td>
<td>...</td>
<td>1.25</td>
<td>6615 8.3 6.7 388 (63)</td>
</tr>
<tr>
<td>OPT</td>
<td>516</td>
<td>...</td>
<td>1.59</td>
<td>3553 11.0 6.9 199 (65)</td>
</tr>
<tr>
<td>Cardiac*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT-D</td>
<td>580</td>
<td>63</td>
<td>0.76</td>
<td>4200 5.5 7.2 284 (48)</td>
</tr>
<tr>
<td>CRT-P</td>
<td>628</td>
<td>63</td>
<td>0.79</td>
<td>4112 5.2 6.5 301 (49)</td>
</tr>
<tr>
<td>OPT</td>
<td>388</td>
<td>75</td>
<td>1.20</td>
<td>2639 8.1 6.8 164 (53)</td>
</tr>
<tr>
<td>HF hospitalizations*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT-D</td>
<td>333</td>
<td>36</td>
<td>0.43</td>
<td>2914 3.8 8.8 166 (28)</td>
</tr>
<tr>
<td>CRT-P</td>
<td>329</td>
<td>33</td>
<td>0.41</td>
<td>2819 3.6 8.6 179 (29)</td>
</tr>
<tr>
<td>OPT</td>
<td>235</td>
<td>46</td>
<td>0.73</td>
<td>1925 5.9 8.2 112 (36)</td>
</tr>
<tr>
<td>Noncardiac</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT-D</td>
<td>339</td>
<td>37</td>
<td>0.44</td>
<td>2430 3.2 7.2 207 (35)</td>
</tr>
<tr>
<td>CRT-P</td>
<td>365</td>
<td>37</td>
<td>0.46</td>
<td>2503 3.2 6.9 222 (36)</td>
</tr>
<tr>
<td>OPT</td>
<td>126</td>
<td>24</td>
<td>0.39</td>
<td>900 2.8 7.1 84 (27)</td>
</tr>
</tbody>
</table>

Note: 2 OPT hospital admissions were classified as unknown. Total follow-up time: CRT-D, 768 years; CRT-P, 793 years; OPT, 324 years.

*Includes nonhospitalized intravenous inotrope/vasoactive therapy >4 hours (intravenous therapy/patients: CRT-D, 11/11; CRT-P, 14/11; OPT 15/15).

Results

Number of Hospital Admissions

Of 1520 patients randomized, 959 (63%) were hospitalized at least once for any cause with the following distribution in the 3 treatment groups: OPT, 199 of 308 (65%); CRT-P, 388 of 617 (63%); and CRT-D, 372 of 595 (63%). A total of 2428 all-cause hospital admissions occurred in these patients. Among these, 1596 (66%) were for cardiac causes, 830 (34%) were for noncardiac causes, and 2 were unspecified.

Baseline Characteristics of Hospitalized Versus Nonhospitalized Patients

No significant differences in baseline characteristics were found between the OPT, CRT-P, and CRT-D groups at randomization as shown previously. Baseline characteristics of hospitalized versus nonhospitalized patients are compared in Table 2. Hospitalized patients were more likely to be male and to have a worse NYHA class, a longer history of HF, ischemic origin, lower systolic blood pressure, lower 6-minute walk distance, and a history of more comorbidities (eg, diabetes mellitus, carotid artery disease, peripheral vascular disease, atrial fibrillation, renal disease, hypertension, and coronary artery bypass graft). Hospitalized patients were less likely to have left bundle-branch block and had a lower use of background therapy such as angiotensin-converting enzyme (ACE) inhibitors and β-blockers. Baseline characteristics of the hospitalized patients also were similar to those who died without being hospitalized, although no formal statistics are shown in Table 2 for that comparison.
All-Cause Hospitalization

After adjustment for follow-up time, the OPT group experienced an average of 1.6 all-cause hospital admissions per patient-year compared with 1.3 and 1.2 in the CRT-P and CRT-D groups, respectively, resulting in a 21% and 25% reduction in the hospitalization rate compared with the OPT group (Table 1 and Figure 2A). Although the percentage of patients hospitalized at least once was very similar in the 3 treatment groups (Table 1), a greater number of multiple hospital admissions per patient-year contributed to the higher...
hospitalization rate in the OPT group. Approximately 34% of the OPT patients had >2 hospital admissions per patient-year compared with 26% of the patients in the combined 2 treatment groups (Figure 2C). The average length of stay in the hospital per patient-year was 11.0 days in the OPT group compared with 8.3 for CRT-P and 8.6 for CRT-D, resulting in a 25% and 22% reduction from the OPT group (Table 1 and Figure 2B). Again, the reason for the higher average number of days in the hospital per patient-year was that more OPT patients were hospitalized for >10 days compared with the CRT groups. Approximately 36% of patients in the OPT group spent >10 days in the hospital per patient-year compared with 28% patients in the combined 2 treatment groups. However, the average length of stay per hospital admission was not different at ≈7 days for each group. Thus, the higher hospitalization burden in the OPT group was due to more multiple hospital admissions.

Cardiac Hospitalization

The percent of all hospital admissions that were cardiac was higher in OPT patients (388 of 516, 75%) compared with CRT-P or CRT-D patients (628 of 993, 63%, and 580 of 919, 63%, respectively). This resulted in an ≈33% reduction in the average number of cardiac hospital admissions per patient-year in the 2 CRT treatment groups compared with OPT (1.2 for OPT, 0.8 for both treatment arms; Table 1 and Figure 2A). Approximately 27% patients in the OPT group compared with 16% each in the 2 CRT groups had ≥2 cardiac hospital admissions per patient-year. The average number of days in the hospital for cardiac causes per patient-year was reduced by 34% in the 2 CRT groups compared with the OPT group (OPT, 8.1 days; CRT-P, 5.2 days; CRT-D, 5.5 days; Table 1 and Figure 2B). However, the average length of stay per hospitalization remained similar (≈7 days) for each group (Table 1).
HF Hospitalization

The percent of hospital admissions for HF also was higher in the OPT group (235 of 516, 46%) compared with both the CRT-P and CRT-D patients (329 of 993, 33%, and 333 of 919, 36%, respectively; Table 1). When hospital admissions for HF were expressed as a percent of cardiac admissions, they remained more frequent in the OPT group (235 of 388, 61%) than in the CRT-P (329 of 628, 52%) and CRT-D (333 of 580, 57%) groups. Thus, the decrease in cardiac hospital admissions was due largely to a decrease in HF hospital admissions. After adjustment for follow-up time, CRT-P was associated with a 44% reduction and CRT-D with a 41% reduction in HF hospital admissions per patient-year compared with the OPT group (0.7 for OPT, 0.4 for both treatment arms; Table 1 and Figure 2A). Fifteen percent of patients in the OPT group had >2 HF hospital admissions per patient-year compared with almost half that in the device treatment groups (9%). The use of CRT-P or CRT-D was associated with a 39% and 36% reduction, respectively, in the number of HF hospitalization days per patient-year (CRT-P, 3.6 days; CRT-D, 3.8 days) compared with OPT (5.9 days). Again, the average length of stay per HF hospital admission was no different for the 3 groups (8.2 days for OPT, 8.6 days for CRT-P, and 8.8 days for CRT-D).

Other Cardiac Hospitalization

After hospitalizations for HF, cardiac procedures were the next most common cardiac cause for hospitalization. The
number of hospital admissions per patient-year for a cardiac procedure was highest for the OPT group (0.24 for OPT, 0.13 for CRT-P, and 0.09 for CRT-D; *P* < 0.01). Of 78 cardiac procedures in the OPT group, 33 (42%) were for CRT implants, 13 (17%) were for electrophysiological studies, 10 (13%) were for pacemaker/defibrillator implants, 5 (6%) were heart transplants, and 15 (19%) were for other causes. In the CRT-P group, 42 of 101 (42%) of procedures were for a lead revision, and 13 of 101 (13%) were to implant a pacemaker or cardioverter-defibrillator. Lead revision was the major cardiac procedure in the CRT-D group (36 of 69, 52%). The other cardiac causes for hospitalizations, excluding HF and cardiac procedure, were unstable angina pectoris, complication of cardiac medication, and atrial arrhythmia. These were not significantly different between the OPT and CRT groups.

### Noncardiac Hospitalization

The average number of hospital admissions per patient-year for noncardiac hospital admissions was 0.39 in the OPT patients compared with 0.46 in CRT-P and 0.44 in CRT-D patients. The average number of days hospitalized per patient-year for noncardiac causes was ∼3 days with an average length of stay per hospital admission of 7 days for all 3 groups. Noncardiac hospitalizations were not significantly higher in the device arms. The most frequent noncardiac hospitalizations included gastrointestinal, pulmonary, and vascular causes.

### Effect of CRT-D and CRT-P on Hospitalizations

The previous description and presentation of hospitalization rates by treatment group take multiple hospital admissions and follow-up time, but not the competing risk of death, into consideration. To provide an unbiased comparison of hospitalization rates between treatment groups, an analysis that considered the competing risk of death, into consideration. To provide an unbiased comparison of hospitalization rates, the device arms. The most frequent noncardiac hospitalizations included gastrointestinal, pulmonary, and vascular causes.

#### Table 3. Factors Associated With Hospitalization Risk for All Patients (Average Risk Ratio and 95% CI)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of renal disease</td>
<td>1.73</td>
<td>1.56</td>
</tr>
<tr>
<td>Heart rate (per 10 bpm higher)</td>
<td>1.12</td>
<td>1.11</td>
</tr>
<tr>
<td>NYHA class IV (vs III)</td>
<td>1.56</td>
<td>1.38</td>
</tr>
<tr>
<td>Ischemic origin</td>
<td>1.47</td>
<td>1.27</td>
</tr>
<tr>
<td>History of PVD</td>
<td>1.56</td>
<td>1.34</td>
</tr>
<tr>
<td>History of AF</td>
<td>1.33</td>
<td>1.23</td>
</tr>
<tr>
<td>LVEF (per 5 % lower)</td>
<td>1.08</td>
<td>1.07</td>
</tr>
<tr>
<td>QRS (per 10 ms lower)</td>
<td>1.03</td>
<td>1.03</td>
</tr>
<tr>
<td>No ACE/ARB and β-blocker use</td>
<td>1.53</td>
<td>1.17</td>
</tr>
<tr>
<td>Systolic BP (per 5 mm Hg lower)</td>
<td>1.03</td>
<td>1.02</td>
</tr>
<tr>
<td>History of CABG</td>
<td>1.31</td>
<td>...</td>
</tr>
<tr>
<td>No β-blocker use</td>
<td>1.39</td>
<td>...</td>
</tr>
<tr>
<td>No ACE/ARB use</td>
<td>1.47</td>
<td>...</td>
</tr>
<tr>
<td>RBBB and/or IVCD vs LBBB</td>
<td>1.26</td>
<td>...</td>
</tr>
<tr>
<td>History of carotid disease</td>
<td>1.33</td>
<td>...</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>1.20</td>
<td>...</td>
</tr>
<tr>
<td>IVCD vs (LBBB or RBBB)</td>
<td>1.24</td>
<td>...</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.17</td>
<td>...</td>
</tr>
<tr>
<td>Diuretics use</td>
<td>1.44</td>
<td>...</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio. A risk ratio > 1 implies a higher risk of hospitalization. Includes all variables significant at *P* < 0.05 (sorted by probability values for multivariate analysis). The following baseline variables were considered: randomized treatment, age, gender, body mass index, NYHA class, ischemic origin, left ventricular ejection fraction (LVEF), systolic blood pressure (BP), diastolic blood pressure, heart rate, QRS, PR interval, left bundle-branch block (LBBB), right bundle-branch block (RBBB), intraventricular conduction delay (IVCD), comorbidities (diabetes mellitus, renal failure, carotid artery disease, peripheral vascular disease (PVD)), hypertension, coronary artery bypass graft (CABG) and atrial fibrillation (AF), and therapy (ACE/angiotensin receptor blocker [ARB], β-blocker, digoxin, diuretics, spironolactone, statins, and aspirin).

became apparent almost immediately after device implantation. The difference in the rate of cardiac hospitalizations became significant by ∼3 months.

#### Predictors of Hospitalization

Table 3 shows the significant (*P* < 0.05) univariate and multivariate baseline variables associated with all-cause hospitalization. In this multivariable analysis, after treatment was controlled for, only a few of the variables were found to be independently associated with the increased likelihood of all-cause hospitalization. These included a lower left ventricular ejection fraction, shorter QRS duration, and lower systolic blood pressure; a higher heart rate and worse NYHA class (IV versus III); ischemic origin; history of renal failure, peripheral vascular disease, and atrial fibrillation; and the lack of the use of ACE inhibitor, angiotensin receptor blocker [ARB], β-blocker, digoxin, diuretics, spironolactone, statins, and aspirin).

#### Discussion

HF remains the most common cause of admission to the hospital in elderly patients, resulting in enormous healthcare...
expenditure. Although clinical trial data have shown that the use of ACE inhibitors, β-blockers, aldosterone antagonists, angiotensin receptor blockers, and digitalis reduces overall hospitalizations, an unbiased evaluation of recurrent hospitalizations has been a challenge because of differential follow-up times between comparison groups and the competing risk of mortality. Moreover, statistical comparisons of hospitalization burden that are not adjusted for follow-up time, mortality, and/or multiple hospitalizations can be biased and misleading. It is not uncommon, however, for these hospitalization analyses to be misused or misinterpreted. For example, despite a highly significant difference in the annual mortality rate between treatment groups (20% for the placebo and 11% for the treatment), the carvedilol prospective randomized cumulative survival (COPERNICUS) study analyzed hospitalization data, ignoring the competing risk of mortality. The valsartan heart failure trial (VAL-HeFT) analyzed hospitalization data, ignoring the competing risk of mortality and differences in follow-up time, the results may have been different.

Why did we use such a complicated statistical method for analyzing recurrent hospitalizations in this study? It is well known that the likelihood of hospitalization and death are related to each other. For example, death removes the sickest patients who are likely to be hospitalized, whereas a hospitalization increases the risk of death and the risk of subsequent hospitalization. Therefore, a difference in hospitalization rate between treatment groups could be due solely to differences in survival rather than a specific effect of the treatment on hospitalizations per se. In the COMPANION trial, OPT plus CRT reduced death rates compared with OPT alone. This would be expected to lower the risk of hospitalizations in the OPT group because the sickest patients died and were no longer followed up. Thus, the treatment effect of the device on hospitalizations is attenuated if an adjustment is not made for the competing risk of death. The method of Ghosh and Lin adjusts the estimates of recurrent hospitalizations for the known differences in death and follow-up time that occurred in the study.

Such an analysis confirmed that the use of CRT was associated with a true reduction in hospitalization. It also demonstrated that the reductions in hospitalizations were similar with the use of either CRT-P or CRT-D. This is important because other studies have suggested that implantable cardioverter-defibrillator therapy may increase HF hospitalizations. In the multicenter automatic defibrillator implantation trial II (MADIT II), use of an implantable cardioverter-defibrillator was associated with a significant increase in first and recurrent HF events (adjusted hazard ratios of implantable cardioverter-defibrillator versus placebo, 1.39 [P=0.02] and 1.58 [P<0.001], respectively). It is possible that if the MADIT II investigators had analyzed the data by taking into account the competing risk of mortality and differences in follow-up time, the results may have been different.

Unlike most other studies, the end-point committee of the COMPANION trial adjudicated all hospitalizations, providing a database of all the causes of hospitalization in patients with moderate to severe HF receiving current standard-of-care therapy. The vast majority (75%) of all hospitalizations in the OPT group were related to cardiac causes, of which 61% were due to worsening HF. HF hospitalizations accounted for 46% of all-cause hospitalizations. The proportion of HF hospitalizations in COMPANION was considerably higher than the 32% in the valsartan arm of VAL-HeFT, 30% in the digoxin arm of Digitalis Investigation Group (DIG) trial, 31% in the high-dose ACE inhibitor arm of Assessment of Treatment with Lisinopril and Survival (ATLAS), and 31% in the metoprolol XL arm of the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) trial, confirming that the COMPANION patients had more severe HF.

The use of CRT-P and CRT-D in COMPANION was associated with 21% and 25% reductions, respectively, in all-cause hospitalization, a 33% reduction with either therapy in cardiac hospitalizations, and 44% and 41% reductions in HF hospitalizations. Most of the decrease in all-cause and cardiac hospitalizations with CRT was due to a decrease in HF hospitalizations, particularly multiple hospitalizations. It is noteworthy that the effect of CRT appeared very early and was sustained throughout the study. As Figure 4 shows, the OPT and CRT curves for hospitalizations for HF began to separate within days after randomization and continued to diverge. This would suggest that CRT therapy helps to slow the progression of the disease within days of device implantation. Such an early effect on HF outcomes has not been reported with any previous drug or device therapy. In contrast to the early beneficial effects on HF hospitalizations, mortality benefit of CRT-D versus OPT was not seen until 9 months after randomization.

No systematic analyses have been undertaken of the predictors of all-cause hospitalizations in patients with severe HF. In this study, history of renal disease, worse NYHA class, ischemic origin, history of atrial fibrillation, lower ejection fraction, lower blood pressure, and lack of ACE inhibitor and β-blocker use were independent predictors of hospitalizations. Interestingly, left bundle-branch block did not predict hospitalization. Indeed, longer QRS interval appeared to protect from hospitalization.

Conclusions

In the COMPANION trial, use of CRT with or without a defibrillator was associated with marked reductions in all-cause, cardiac, and HF hospitalization rates in patients with advanced HF in an analysis that accounted for the competing risk of mortality and unequal follow-up time. The benefit is most marked on hospitalizations for HF that appears very early and was sustained.

Source of Funding

The COMPANION study was fully funded by Boston Scientific Corp, CRM division (Guidant Corp).

Disclosures

Drs Kosorok and Song had a contract through the University of Wisconsin with Guidant for the statistical support for COMPANION. Dr DeMets has numerous consulting activities with industry, the National Institutes of Health, and the Food and Drug Administration. In particular, he had a contract through the University of Wisconsin with Guidant for the statistical support for COMPANION. Dr Boehmer...
References


In clinical trials, the true and unbiased assessment of a therapy on hospital admissions is confounded by the competing risk of death and differential follow-up times between treatment groups. To overcome this challenge, we used a novel nonparametric analysis that accounts for multiple hospital admissions, unequal follow-up times between treatment groups, and death as a competing risk in the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) Trial. The analysis showed that cardiac resynchronization therapy with or without a defibrillator was associated with marked reductions in all-cause, cardiac, and heart failure hospitalization rates in patients with advanced heart failure.
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