Journal of the American College of Cardiology Vol. 46, No. 12, 2005

Published by Elsevier Inc.
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2005.09.016

Mode of Death in Advanced Heart Failure

The Comparison of Medical, Pacing, and Defibrillation Therapies in Heart Failure (COMPANION) Trial

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OBJECTIVES The aim of this study was to evaluate the mode of death in patients with advanced chronic heart failure (HF) and intraventricular conduction delay treated with optimal pharmacologic therapy (OPT) alone or OPT with biventricular pacing to provide cardiac resynchronization therapy (CRT) or CRT + an implantable defibrillator (CRT-D).

BACKGROUND Limited data are available on mode of death in advanced HF. No data have existed on mode of death in these patients who also have an intraventricular conduction delay and are treated with CRT or CRT-D.

METHODS Using prespecified definitions and source materials, seven cardiologists assessed mode of death among the 313 deaths that occurred in the Comparison of Medical, Pacing, and Defibrillation Therapies in Heart Failure (COMPANION) trial.

RESULTS A primary cardiac cause was present in 78% of deaths. Pump failure (44.4%) was the most common mode of death followed by sudden cardiac death (SCD) (26.5%). Compared with OPT, CRT-D significantly reduced the number of cardiac deaths (38%, $p = 0.006$), whereas CRT alone was associated with a non-significant 14.5% reduction ($p = 0.33$). Both CRT and CRT-D tended to reduce pump failure deaths (29%, $p = 0.11$ and 27%, $p = 0.14$, respectively). The CRT-D significantly reduced SCD (56%, $p = 0.02$), but CRT alone did not.

CONCLUSIONS Pump failure deaths are the predominant mode of death in patients with advanced HF and are modestly reduced by both CRT and CRT-D. Only CRT-D reduced SCD and thus produced a favorable effect on cardiac mortality. (J Am Coll Cardiol 2005;46:2329–34)

Chronic heart failure (HF) is characterized by a progressive course of increasing symptoms, recurrent hospitalizations, and shortened survival, all likely mediated by ventricular "remodeling"(1). Advances in HF therapy, principally neurohormonal blockade, have reduced the annual mortality in patients with mild to moderate HF from nearly 16% to 6% to 8% (2–9). However, recent trials of further additive pharmacologic therapy have been largely disappointing (9–12). Moreover, in advanced HF, annual mortality rates with successful therapies (11.25%—beta blocker in Carvedilol Prospective Randomized Cumulative Survival Study [COPERNICUS] [7], 17.5%—aldosterone antagonist in Randomized Aldactone Evaluation Study [RALES] [8]) suggest limitations of currently available medical therapy. To further improve prognosis, two electrophysiologic device-related therapies have been evaluated in HF: 1) intracardiac defibrillation therapy (implantable cardioverter-defibrillator [ICD]) targeting ventricular arrhythmias; and 2) cardiac resynchronization therapy (CRT), targeting ventricular dyssynchrony. The Comparison of Medical, Pacing, and Defibrillation Therapies in Heart Failure (COMPANION) trial (13) tested both CRT and CRT + ICD (CRT-D) in an advanced HF population with a prolonged QRS. Study results showed that time to all-cause mortality was reduced by 24% with CRT and by 36% with CRT-D when compared with optimal pharmacologic therapy (OPT).

Mode of death analysis provides an understanding of the clinical course of the disease in the study population and

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Manuscript received March 1, 2005; revised manuscript received August 24, 2005, accepted September 8, 2005.

Abbreviations and Acronyms

CI	= confidence interval
COMPANION	= Comparison of Medical, Pacing, and Defibrillation Therapies in Heart Failure trial
CRT	= cardiac resynchronization therapy
CRT-D	= cardiac resynchronization therapy with defibrillator
HF	= heart failure
HR	= hazard ratio
ICD	= implantable cardioverter-defibrillator
NYHA	= New York Heart Association
OPT	= optimal pharmacologic therapy
SCD	= sudden cardiac death

offers insights into mechanism of action of the therapeutic modality. This analysis was undertaken to examine the mode of death in a group of patients with advanced HF from the COMPANION study in order to better understand the manner of potential benefit from therapy with CRT and CRT-D.

METHODS

The COMPANION study was a randomized, placebo-controlled trial that tested the hypothesis that CRT and CRT-D would reduce the risk of death and hospitalization in patients with advanced HF and prolonged intraventricular conduction (14). A total of 1520 patients in New York Heart Association (NYHA) functional 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, or CRT-D. All post-randomization deaths, with the exception of post-cardiac transplantation deaths, were counted as study end points and were adjudicated and classified.

All analyses were by intention to treat. Time to cause-specific death was plotted using the Kaplan-Meier method, and differences between groups were determined by the log-rank statistic. Cox proportional-hazards regression models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs). Details regarding data collection and censoring for the time to event analyses are described elsewhere (13). All p values are two-sided and nominal.

Mortality definitions. CAUSE OF DEATH. The primary mode of death refers to the event that led to death. Deaths were classified as cardiac or non-cardiac, with more specific categories assigned as permitted by the circumstances of the clinical event. For the most common specific categories: sudden cardiac death (SCD) was defined as observed or unobserved but assumed to be instantaneous because of the clinical setting (SCD was further classified as with or without worsening HF); pump failure death was defined as a progressive HF course manifested by symptoms requiring increased medications, including intravenous agents (pump failure death was further classified as progressive deterioration or recurrent hospitalization).

RESULTS

Baseline characteristics of the COMPANION trial patients have been published previously (13). In brief, the patient group studied had a median age of 69 years, 86% were in NYHA functional class III and 14% in class IV, with a median ejection fraction of 21%. The median QRS duration was 160 ms, and 70% had left bundle-branch block. All patients were required by protocol to be on OPT (89% on angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, 68% on beta-blockers, 55% on spironolactone).

Overall cohort. The adjudicated causes of death for the entire cohort are shown in Table 1. Overall, a cardiac cause of death was noted in 78% of patients. Pump failure was the most common cause of death (44.4%) followed by SCD (26.5%). When the analysis was carried out separately on the non-device OPT group, there were 44.2% pump failure and 23.4% SCDs.

Treatment groups. Mode of death for the three treatment groups is shown in Table 1. Kaplan-Meier curves for cardiac and non-cardiac deaths are shown in Figures 1A and 1B. There were significantly fewer cardiac deaths in the CRT-D arm as compared with OPT ($p = 0.006$), but there was no difference between the CRT and OPT groups. Non-cardiac deaths did not differ between treatment groups.

Table 1. Mode of Death Overall, and Within Each Treatment Group

Cause of Death	OPT n (%*) [%†]	CRT n (%*) [%†]	CRT-D n (%*) [%†]	Overall n (%*) [%†]
Number of patients	308	617	595	1,510
Cardiac	54 (18.8) [75.3]	109 (17.1) [83.2]	76 (12.8) [72.4]	243 (16.1) [77.6]
SCD	18 (5.8) [23.4]	48 (7.8) [36.6]	17 (2.9) [16.2]	83 (5.5) [26.5]
Pump failure	34 (11.0) [44.2]	53 (8.6) [40.5]	52 (8.7) [49.5]	139 (9.1) [44.4]
Ischemic	4 (1.3) [5.2]	2 (0.3) [1.5]	4 (0.7) [3.8]	10 (0.7) [3.2]
Cardiac procedure	2 (0.6) [2.6]	6 (1.0) [4.6]	2 (0.3) [1.9]	10 (0.7) [3.2]
Others	0 (0) [0]	0 (0) [0]	1 (0.2) [1.0]	1 (0.1) [0.3]
Vascular	0 (0) [0]	5 (0.8) [3.8]	3 (0.5) [2.8]	8 (0.5) [2.6]
Non-cardiac	11 (3.6) [14.3]	14 (2.3) [10.7]	21 (3.5) [20.0]	46 (3.0) [14.7]
Unknown	8 (2.6) [10.4]	3 (0.5) [2.3]	5 (0.8) [4.8]	16 (1.0) [5.1]
Total	77 (25.0)	131 (21.2)	105 (17.6)	313 (20.6)

*% of deaths by randomized patients within each group. †% of deaths within each treatment group.
CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy with defibrillator; OPT = optimal pharmacologic therapy; SCD = sudden cardiac death.

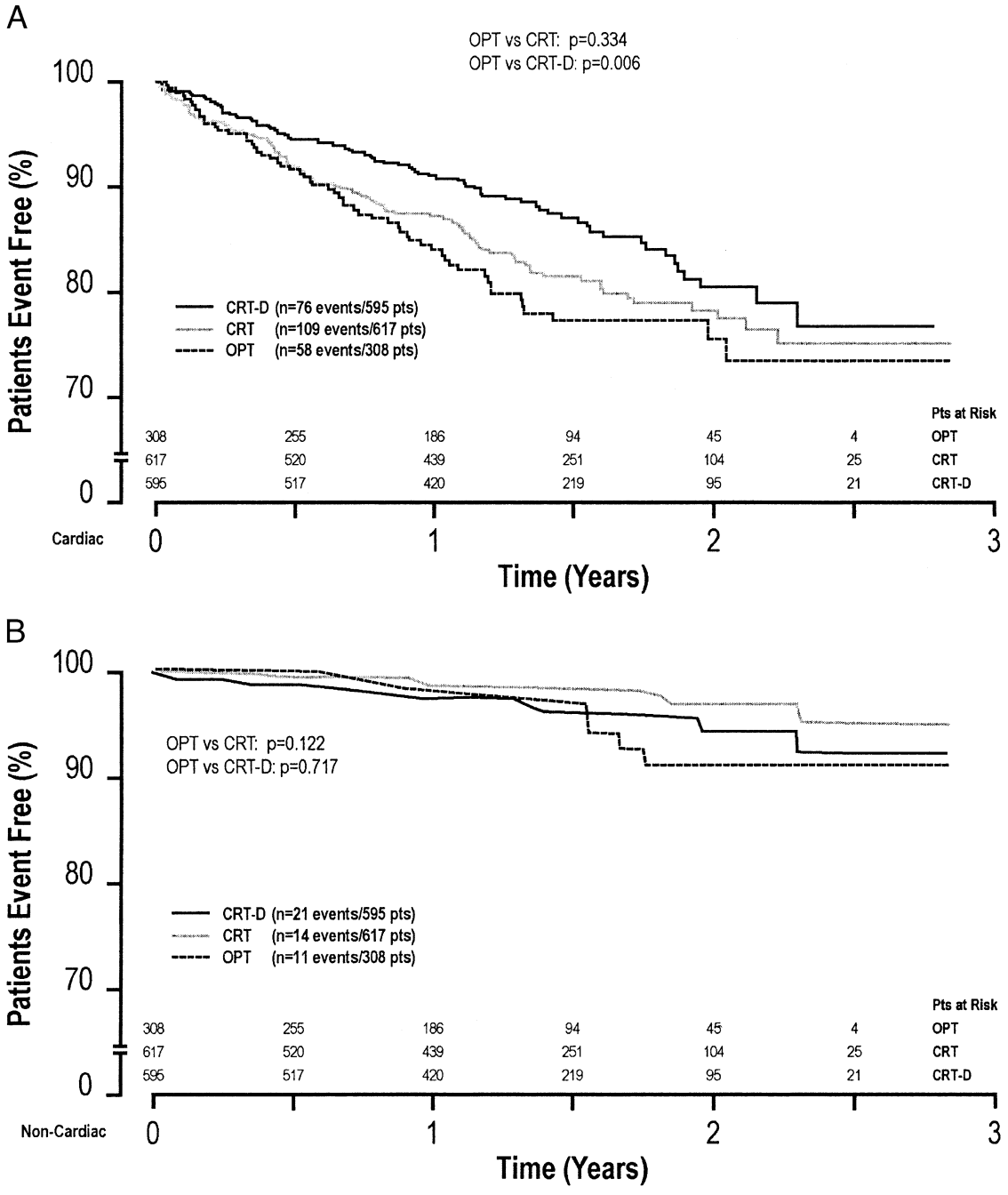

Figure 1. **(A)** Kaplan-Meier estimates of the time to first cardiac death. **(B)** Kaplan-Meier estimates of the time to first non-cardiac death. CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy with defibrillation; OPT = optimal pharmacologic therapy.

As in the overall cohort, the two most common modes of cardiac deaths were pump failure and SCD. Other causes such as ischemia were infrequent (Table 1). Kaplan-Meier curves for pump failure and SCDs are shown in Figures 2 and 3. As compared with OPT, there was a non-significant reduction of pump failure deaths in both the CRT (HR 0.71, 95% CI 0.46 to 1.09, p = 0.11) and CRT-D (HR 0.73, 95% CI 0.47 to 1.11, p = 0.15) groups. For CRT grouped together (CRT and CRT-D), pump failure deaths were decreased by 29% (HR 0.71, 95% CI 0.48 to 1.05, p = 0.08). For SCD, there was a significant, 56% reduction in deaths in the CRT-D arm as compared with OPT (HR 0.44, 95% CI 0.23 to 0.86, p = 0.02), whereas no reduction was seen with CRT as compared with OPT (HR 1.21, 95% CI 0.7 to 2.07, p = 0.50).

DISCUSSION

The data from the COMPANION trial provide an opportunity to examine the mode of death in an advanced HF population as well as the effect of device therapies.

Mode of death analysis. Mode of death analysis has been undertaken in major HF trials and most, like the COMPANION trial, have used a committee to adjudicate events. The results, shown in Table 2, demonstrate that the

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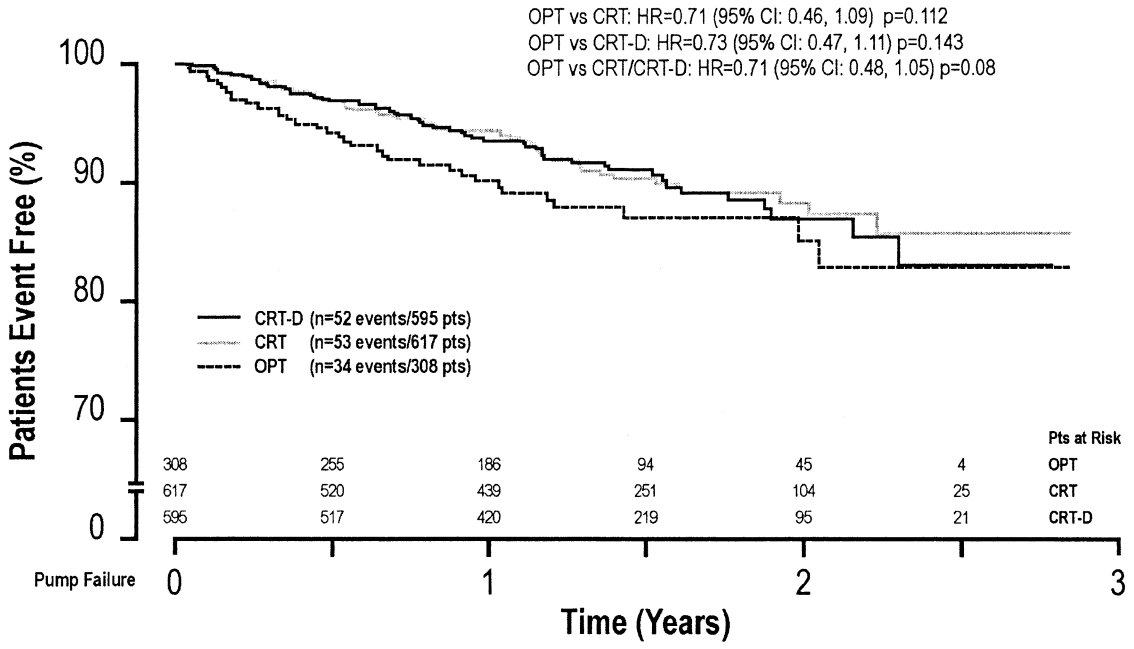

Figure 2. Kaplan-Meier estimate of the time to first pump failure death. CI = confidence interval; HR = hazard ratio; other abbreviations as in Figure 1.

majority of deaths were of cardiovascular cause, predominantly sudden and pump failure events. The relative proportion of these events differs according to the severity of HF and is relevant as they represent different therapeutic targets. In mild-moderate HF, particularly with angiotensin-converting enzyme inhibitor and beta-blocker therapy, sudden deaths are the most common cause of death and pump failure deaths are less frequent (Metropolol CR/XL randomized intervention trial in congestive heart failure [MERIT-HF] 1.5%/year; Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity [CHARM] Added program 2.0%/year) (6,15). The implications are significant for clinical trials in that interventions that decrease sudden deaths without any influence on pump failure can reduce total mortality, as in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) (15). Conversely, in the Valsartan Heart Failure Trial (Val-HeFT) (53% sudden deaths), valsartan did not decrease sudden deaths and therefore did not influence overall mortality (9). In more advanced HF, where pump failure deaths are more frequent, the therapeutic target is more complex and interventions need to additionally reduce pump failure deaths to

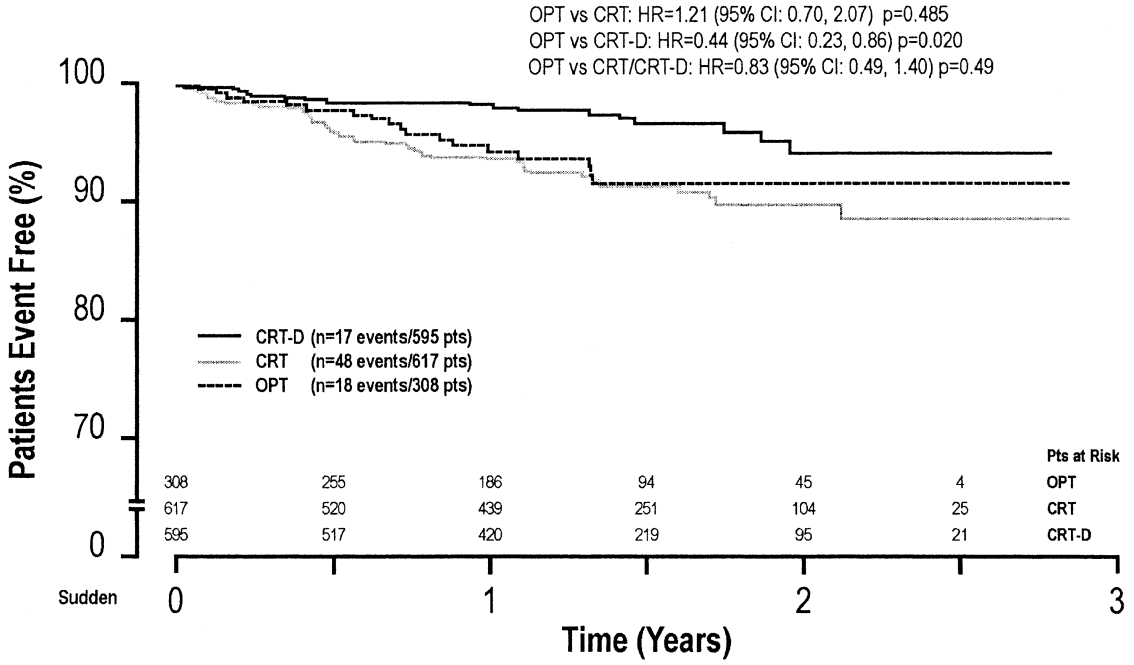

Figure 3. Kaplan-Meier estimate of the time to first sudden cardiac death. Abbreviation as in Figure 1.

Table 2. Mode of Death in Selected Heart Failure Trials

Trials	Total Study N	Total Mortality n (%)	Annual Mortality Rate (%)	Cardiovascular Death n (%*) [%†]	Sudden Death n (%*) [%†]	Pump Failure Death n (%*) [%†]	Myocardial Infarction n (%*)
CONSENSUS-1	253	118 (46.6)	33 (6 mos)	117 (99.1) [46.2]	39 (33.3) [15.4]	66 (55.9) [26.1]	3 (2.5)
SOLVD-T	2,569	962 (37.4)	11.6	860 (89.4) [33.5]	218 (22.7) [8.5]	460 (47.8) [17.9]	93 (9.7)
V-HeFT	642	283 (44.1)	16	267 (94.3) [41.6]	164 (58.0) [25.5]	89 (31.4) [13.9]	14 (4.9)
V-HeFT 11	804	285 (35.4)	11	249 (87.4) [30.9]	149 (52.3) [18.5]	90 (31.6) [11.2]	10 (3.5)
CHF-STAT	674	274 (40.7)	14.9	229 (83.6) [33.9]	139 (50.7) [20.6]	74 (27.0) [10.9]	No data
DIG study	6,800	2,375 (34.9)	11.3	2,020 (85.1) [29.7]	952 (40.1) [14]	843 (35.3) [12.4]	No data
PRAISE	1,153	413 (35.8)	30.8	368 (89.1) [31.9]	185 (44.8) [16]	165 (40.0) [14.3]	12 (2.9)
MERIT-HF	3,991	362 (9.7)	10	331 (91.4) [8.3]	211 (58.3) [5.3]	88 (24.3) [2.2]	No data
MERIT-HF-BB	1,990	145 (7.2)	7.3	128 (88.2) [6.4]	79 (54.4) [3.9]	30 (20.8) [1.5]	No data
ValHeFT	5,010	979 (19.5)	9.5	No data	520 (53.1) [10.4]	243 (24.8) [4.9]	No data
CHARM-Alt	2,028	561 (27.6)	7.5	471 (83.9) [23.2]	191 (34) [9.4]	159 (28.3) [28.3]	51 (9.1)
CHARM-Add	2,548	789	7.5	649 (82.3) [25.5]	318 (40.3) [12.5]	208 (26.4) [8.2]	39 (4.9) [1.5]
CARE-HF	813	202 (24.8)	12.6	143 (71) [17.6]	67 (33.1) [8.2]	89 (44.1) [10.9]	No data
BEST	2,708	860	16.6	731 (85) [26.9]	385 (44.8) [14.2]	262 (30.5) [9.7]	23 (2.7)
VEST	3,833	802	24.1	750 (93.5) [19.6]	410 (51.1) [10.7]	321 (40) [8.4]	19 (2.4)
RALES	1,663	670 (40.2)	23	540 (80.5) [32.5]	192 (28.6) [11.5]	316 (47.1) [19]	32 (4.8)

*% of deaths by all deaths in each trial; †% of deaths by randomized patients in each trial.

BEST = Beta-Blocker Evaluation Survival Trial; CARE-HF = CArdiac REsynchronization in Heart Failure; CHARM-Add = Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity-Added; CHARM-Alt = Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity-Alternative; CHF-STAT = Amiodarone in Patients with Congestive Heart failure and Asymptomatic Ventricular Arrhythmia; CONSENSUS-1 = Effects of Enalapril on Mortality in Severe Congestive Heart failure; DIG = Digoxin Investigation Group; MERIT-HF = Metropolol CR/XL Randomized Intervention Trial in congestive Heart Failure; MERIT-HF-BB = Metropolol CR/XL Randomized Intervention Trial in Congestive Heart Failure-Beta-Blocker arm; PRAISE = Placebo-Controlled Study to Evaluate the Effects of Amlodipine on Mortality and Morbidity in Patients with Severe Heart Failure; RALES = Randomized Aldactone Evaluation Study; SOLVD-D = Studies of Left Ventricular Dysfunction; ValHeFT = Valsartan Heart Failure Trial; VEST = Vesnarinone Evaluation of Survival Trial; V-HeFT II = Vasdilator in Heart Failure Trial.

be successful therapies. In SCD-HeFT the subgroup analysis of NYHA functional class III patients did not show overall mortality benefit (16). The CARE-HF (17) results are also illustrative—pump failure deaths comprised the majority of events, and while CRT patients experienced fewer sudden and pump failure deaths, the largest reduction (42%) was in the latter events.

The patient group in the COMPANION trial was a particularly high-risk HF cohort with a wide QRS interval but also a previous HF hospitalization within 12 months. The predominance of pump failure deaths represented an important therapeutic target, and therefore a device that would target both progressive HF and arrhythmic deaths would have the greatest likelihood of success as noted in the overall COMPANION trial results.

Two other points are worth noting on mode of death. 1) Non-cardiac deaths were not altered by therapy within the overall trial despite a 36% reduction in overall mortality in CRT-D. Such findings raise the question of whether non-cardiac or non-cardiovascular deaths should be included in trials testing cardiovascular interventions, because these events would provide background noise in an all-cause mortality analysis and dilute a treatment effect on cardiovascular events. Similar findings on noncardiovascular deaths led the CHARM authors to recently suggest that cardiovascular deaths might be a more appropriate end point for trials testing cardiovascular interventions. 2) Myocardial infarctions are an infrequent adjudicated cause of death in HF. Whether these events are undercounted because patients expire before evaluation is uncertain. An analysis by Uretsky (18) suggested an underdiagnosis of myocardial infarction using autopsy data from the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial where evidence of acute ischemic events was more commonly seen in deaths classified as sudden than clinical data indicated. Future device trials may provide data on the extent to which myocardial infarctions are present in patients in whom ICD therapy prevented SCD.

CRT and CRT-D effect. Although either CRT device had a beneficial effect on the progression of HF including a 29% decrease in pump failure deaths, the principal mortality benefit of the COMPANION trial was seen in reduction of SCD when CRT was combined with a defibrillator. The SCD reduction supports previous findings of the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) (19) (post-myocardial infarction ischemic cardiomyopathy), and the more recent SCD-HeFT (16). Sudden cardiac deaths were not decreased in the CRT group, and while the point estimate appears unfavorable, wide confidence intervals make interpretation uncertain. Further, other available data do not support an increased risk for SCD with the use of CRT. Electrical dispersion has been noted in some left ventricular pacing animal models, but biventricular pacing does not produce this effect (20). Chronic controlled human studies with CRT therapy do not demonstrate an increased risk of ICD shocks compared with controls (21). Finally, in the CARE-HF study (17), CRT reduced SCD although the larger reduction was in pump failure deaths.

It is of interest to note that the SCD curves separate later than the pump failure curves in the COMPANION trial. The relatively late separation of SCD curves has been noted in both the MADIT-II (19) and SCD-HeFT (16) trials. Moss et al. (22) addressed this phenomenon in the MADIT-II trial and, at least in part, ascribed it to an early preponderance of non-SCD events. This would be a potential explanation for the COMPANION trial results because

SCD were the minority of fatal events. For pump failure deaths, the earlier curve separation and beneficial trend from CRT in the COMPANION trial is consistent with previous reports of improvement in cardiac size and function (23,24) with the CRT modality, as well as the benefit in combined death and HF morbidity previously reported in the COMPANION trial (13) and now also in CARE-HF (17).

Study limitations. Because most SCDs were not witnessed, information directly describing the events is limited. However, the course of these patients and the nature of the events were carefully considered in choosing this category. When "sudden cardiac death" was assessed, little or no interval worsening of HF occurred and the death was considered unexpected. In some cases where crossover from OPT to device occurred, the patient withdrew consent for study and for any further follow-up. Therefore the number of deaths classified as "unknown" was greater than in other recent trials. Comparisons of time curves involving modes of death are difficult owing to the concept of competing risk and the relative numbers of events.

Conclusions. In advanced HF with wide QRS interval, pump failure is the predominant cause of death. Cardiac resynchronization therapy modestly reduces this outcome. The CRT-D device additionally reduces SCD, resulting in significant reductions in cardiac and all-cause mortality. These data support the conclusion of the COMPANION trial that the optimal therapy for patients with advanced HF and a wide QRS interval is CRT-D in addition to maximum tolerated medical therapy.

Acknowledgments

We would like to thank all the physicians and patients for their dedication to advancing the treatment of HF through participation in the COMPANION trial. We also appreciate the collaborative efforts of the following institutions: Executive Committee—M. Bristow (co-chair), A. Feldman (co-chair), L. Saxon, T. DeMarco, D. Kass, J. Boehmer, D. Mann, S. Singh; Biostatisticians (University of Wisconsin)—D. DeMets, S. Anderson, J. Barnet, M. Gruber; Guidant Clinical Staff—D. DeVries, L. Voshage-Stahl, P. Yong, D. Breiter, L. Galle, F. Ecklund, J. Leigh.

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