Predictors of Sudden Cardiac Death and Appropriate Shock in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Trial

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Background—The factors that determine the risk for sudden death or implantable cardioverter defibrillator therapy in patients receiving cardiac resynchronization therapy (CRT) therapies are largely unknown.

Methods and Results—We hypothesized that clinical measures of heart failure severity and the presence of comorbid conditions would predict the risk of malignant arrhythmias in the 1520 patients enrolled in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Trial. Outcomes in the CRT group after implantable cardioverter defibrillator therapy were also evaluated. The CRT-defibrillator device reduced the risk of sudden death by 56% compared with drug therapy (17 of 595 [2.9%] versus 18 of 308 [5.8%], P<0.02). CRT therapy was not associated with sudden death risk reduction (48 of 617 [7.8%]). Other factors associated with reduced sudden death risk were left ventricular ejection fraction >20% (HR, 0.55 [95% CI, 0.35 to 0.87]; P=0.01), QRS duration >160 ms (HR, 0.63 [95% CI, 0.40 to 0.997]; P=0.05), and female gender (HR, 0.56 [95% CI, 0.34 to 0.94]; P=0.003). The risk for sudden death was increased by advanced New York Heart Association class IV heart failure (HR, 2.62 [95% CI, 1.61 to 4.26]; P<0.011) and renal dysfunction (HR, 1.69 [95% CI, 1.06 to 2.69]; P=0.03). An appropriate shock was experienced in 88 (15%) of the 595 CTR-D patients. In the CRT-defibrillator patients, female gender (HR, 0.54 [95% CI, 0.31 to 0.94]; P=0.03) and use of neurohormonal antagonists were associated with reduced risk. Class IV heart failure status increased risk. Appropriate implantable cardioverter defibrillator therapy was positively associated with risk of death or all-cause hospitalization (HR, 1.57; P<0.002), pump failure death or hospitalization (HR, 2.35; P<0.001), and sudden death (HR, 2.99; P=0.03), but not total mortality (HR, 1.3; P=0.28).

Conclusions—In CRT candidates, sudden cardiac death risk is associated with higher New York Heart Association class and renal dysfunction. In CRT-defibrillator recipients, reduction in the risk of an appropriate shock is associated with medical therapy with neurohormonal antagonists, female gender, and New York Heart Association functional class III versus IV clinical status. Shock therapy was associated with worse outcome. (Circulation. 2006;114:2766-2772.)

Key Words: arrhythmia ■ death, sudden ■ defibrillation ■ electrophysiology ■ heart failure ■ implantable cardioverter-defibrillators

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was reduced by 63% with CRT-D therapy (unadjusted HR, 0.37 [95% CI, 0.21 to 0.65]; P=0.01). The absolute rates for sudden cardiac death were CRT-D, 17 of 595 (2.9%); CRT, 48 of 617 (7.8%); and optimized pharmacological therapy (OPT), 18 of 308 (5.8%). Comparing OPT as baseline therapy, there was a benefit with addition of CRT-D therapy

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Dear Reader,

The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Trial demonstrated that cardiac resynchronization therapy (CRT) decreases the combined risk of death or first hospitalization in patients with advanced heart failure (HF) and QRS prolongation.1 Although there was no significant difference in overall mortality (hazard ratio [HR], 0.84) between CRT and CRT with implantable cardioverter defibrillator (ICD) therapy (CRT-D), sudden death
(unadjusted HR, 0.45 [95% CI, 0.23 to 0.86], \( P = 0.02 \)) but not CRT therapy (unadjusted HR, 1.21 [95% CI, 0.70 to 2.08], \( P = 0.50 \)).

There is very little available data that identify baseline predictors for sudden death or that describe the time course to appropriate ICD therapy in HF patients with ICD or CRT-D devices implanted for primary prevention indications.\(^2\)\(^-\)\(^8\)

Factors influencing survival benefit or likelihood of ICD therapy that have been identified include greater time duration after myocardial infarction, higher New York Heart Association (NYHA) functional class, and lower left ventricular ejection fraction (LVEF).\(^3\)\(^-\)\(^5\)

For primary prevention CRT-D recipients, early studies with short durations of follow-up did not show a reduction in device therapies for ventricular tachycardia (VT) or ventricular fibrillation (VF) for the first 6 months after implantation regardless of whether CRT was programmed on or off.\(^6\)\(^-\)\(^8\) The influence of CRT therapy on arrhythmia outcomes is also largely unknown for CRT recipients without a history of symptomatic ventricular arrhythmias. In 2 other controlled mortality trials that studied patients treated only with CRT, 1 did not report mode of death after 6 months of CRT and the other showed a 40% reduction in sudden death risk when follow-up was extended to 3 years after implant.\(^9\)\(^-\)\(^11\)

A post hoc analysis was performed based on the hypothesis that both the severity of HF and presence of comorbidities would predict a higher likelihood for sudden death and, in ICD recipients, ventricular arrhythmias requiring defibrillation.

The impact of ICD therapies on outcomes after CRT was also assessed.

Methods

The trial design and results of the COMPANION Trial have been reported elsewhere.\(^1\) The trial prospectively enrolled 1520 patients with NYHA class III or IV HF due to ischemic or nonischemic cardiomyopathy in association with a LVEF of \( \leq 0.35 \) and a QRS interval of \( \geq 120 \) ms and was hospitalized for the treatment of HF in the year before enrollment. No patient had a history of a symptomatic ventricular arrhythmia. Patients were randomly assigned in a 1:2:2 ratio to protocol-mandated (OPT) alone or in association with a CRT or CRT-D device. Pharmacological therapy required maximally tolerated dosages of diuretics, angiotensin-converting enzyme inhibitors, \( \beta \)-blockers, and spironolactone. The primary composite end point risk of time to death or hospitalization from any cause was reduced by 20% in both CRT and CRT-D arms compared with pharmacological therapy. The relative risk of all-cause mortality was reduced by 36% with the CRT-D device \( (P = 0.003) \) and 24% with CRT \( (P = 0.06) \).

All 1520 study patients were included in the post hoc analysis of baseline predictors of risk for sudden cardiac death, and all 595 CRT-D patients were included in the appropriate shock analysis. Sudden cardiac death events were adjudicated by an end points committee that determined mode of death according to published definitions.\(^2\)\(^-\)\(^5\) In the 595 patients randomized to the CRT-D device, appropriate device therapy consisting of an ICD shock was also analyzed. Shocks were designated as appropriate after the implanting physician reviewed the intracardiac electrograms stored from the event and determined that a shock was delivered for VT/VF meeting the programmed detection parameters.

A Cox proportional hazards multivariate regression model with stepwise selection was used for time to sudden cardiac death and appropriate shock analysis. Date of appropriate shock was determined according to the date the shock was reported. All HRs are adjusted unless indicated (unadjusted). The following baseline variables were included in the stepwise selection: NYHA class (IV versus III), LVEF (>20% versus \( \leq 20\% \)), \( \beta \)-blocker, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, and spironolactone use, QRS > 160 ms, left bundle-branch block, right bundle-branch block, heart rate \( \leq 72 \) bpm, ischemic etiology, female gender, diabetes, age \( \leq 65 \) years, body mass index, and the presence of renal dysfunction. Variables remained in the model if they were significant at 0.05 (entry criteria \( = 0.30 \)). All analyses were based on intent-to-treat. Based on the log(-log) plot, there was no evidence that the proportional hazards assumption was violated for the sudden cardiac death analysis by treatment. For the composite mortality and hospitalization analysis, any hospitalization end point and associated follow-up time prior to the shock are excluded in the “appropriate shock” arm.

The number needed to treat is calculated at the median follow-up time of 12 months for the mortality and hospitalization end points, and 15 months for the mortality only end points. The needed to treat calculation is the reciprocal of the absolute risk reduction multiplied by 100. The absolute risk reduction is the difference between the percent of patients who are end point–free at the median follow-up time in the treatment arm and the same percentage in the OPT arm. The resulting statistic is the number of patients who must be treated for one person to benefit.\(^12\)

The clinical characteristics reflective of HF severity and comorbidities used in this analysis to assess their relationship to risk are provided in Table 1. There were no significant differences in any of the prespecified variables according to treatment group.

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

### TABLE 1. Clinical Characteristics Evaluated for Risk of Sudden Death and Appropriate ICD Shock

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>OPT (n=308)</th>
<th>CRT (n=617)</th>
<th>CRT-D (n=595)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA heart failure class</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class III, %</td>
<td>82</td>
<td>87</td>
<td>86</td>
<td>0.11*</td>
</tr>
<tr>
<td>Class IV, %</td>
<td>18</td>
<td>13</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>LVEF measurement, %</td>
<td>23(\pm)7.2</td>
<td>22(\pm)6.8</td>
<td>23(\pm)6.9</td>
<td>0.20†</td>
</tr>
<tr>
<td>mean(\pm)SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF cause, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>59</td>
<td>54</td>
<td>55</td>
<td>0.34*</td>
</tr>
<tr>
<td>Nonischemic</td>
<td>41</td>
<td>46</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm, mean(\pm)SD</td>
<td>72(\pm)12</td>
<td>73(\pm)13</td>
<td>73(\pm)13</td>
<td>0.48†</td>
</tr>
<tr>
<td>Age, y, mean(\pm)SD</td>
<td>67(\pm)11</td>
<td>65(\pm)12</td>
<td>66(\pm)11</td>
<td>0.19</td>
</tr>
<tr>
<td>Gender, % female</td>
<td>31</td>
<td>33</td>
<td>33</td>
<td>0.92*</td>
</tr>
<tr>
<td>Body mass index, mean(\pm)SD</td>
<td>28(\pm)6.2</td>
<td>28(\pm)6.0</td>
<td>29(\pm)6.2</td>
<td>0.13</td>
</tr>
<tr>
<td>Diabetes status, %</td>
<td>45</td>
<td>39</td>
<td>41</td>
<td>0.23*</td>
</tr>
<tr>
<td>Renal dysfunction, %</td>
<td>23</td>
<td>22</td>
<td>23</td>
<td>0.95</td>
</tr>
<tr>
<td>( \beta )-Blocker, %</td>
<td>66</td>
<td>68</td>
<td>68</td>
<td>0.85*</td>
</tr>
<tr>
<td>ACE inhibitor, %</td>
<td>69</td>
<td>70</td>
<td>69</td>
<td>0.94*</td>
</tr>
<tr>
<td>Angiotensin receptor blocker, %</td>
<td>23</td>
<td>22</td>
<td>23</td>
<td>0.98*</td>
</tr>
<tr>
<td>Spironolactone, %</td>
<td>55</td>
<td>53</td>
<td>55</td>
<td>0.80*</td>
</tr>
<tr>
<td>QRS duration, ms, mean(\pm)SD</td>
<td>156(\pm)24</td>
<td>159(\pm)25</td>
<td>159(\pm)24</td>
<td>0.21†</td>
</tr>
<tr>
<td>Left bundle-branch block, %</td>
<td>70</td>
<td>69</td>
<td>73</td>
<td>0.22*</td>
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<tr>
<td>Right bundle-branch block/WCD, %</td>
<td>30</td>
<td>31</td>
<td>27</td>
<td></td>
</tr>
</tbody>
</table>

\( * \)P value based on \( \chi^2 \) test. The contrasts pertain to differences between any of the treatment groups.

\( † \)P value based on \( t \) test. The contrasts pertain to differences between any of the treatment groups.

ACE indicates angiotensin-converting enzyme; IVCD, intraventricular conduction delay.
Results
Unanticipated Crossovers and Study Withdrawals
Implant success of the CRT system was achieved in 87% of CRT and 91% of CRT-D patients. During the course of the study, a total of 113 (37%) OPT-treated, 67 (11%) CRT-treated, and 17 (3%) CRT-D–treated patients crossed over from their treatment arms to receive a commercially available pacemaker, CRT, or CRT-D device for arrhythmia or HF indications. In this group, there were a total of 3 sudden deaths, 1 in each randomization arm. Before crossing over, the majority of patients had reached a primary study end point: 103 (91%) OPT patients, 53 (79%) CRT patients, and 6 (35%) CRT-D) patients.

Sudden Death
Over a mean follow-up of 15.7 months, sudden death was adjudicated as the cause of death in 18 of 308 (5.8%) patients randomized to OPT, 48 of 617 (7.8%) patients who received the CRT device, and 17 of 595 (2.9%) patients with the CRT-D device. Compared with OPT, the CRT-D device was associated with a 55% reduction in sudden death risk (HR, 0.45; P=0.02). Table 2 lists the HRs for those variables associated with either a reduction or increased risk of sudden death. These are based on 83 sudden deaths occurring in 1519 patients. Along with CRT-D therapy, LVEF $\geq 20\%$, QRS duration at baseline $\geq 160$ ms, and female gender were associated with reduced risk. Conversely, class IV versus class III HF status increased risk. Likewise, the presence of renal dysfunction increased sudden death risk.

Appropriate Shock
ICD therapy of a first shock was delivered in 142 of 595 patients (24%). Of these, 88 (61%) were considered appropriate for sensed VT or VF and 54 (38%) were classified as inappropriate because of either supraventricular tachycardia (42 events), oversensing (10 events), or unclassified reasons (2 events). The time to device shock is shown in Figure 1 and illustrates that nearly 1 in 5 patients randomized to CRT-D therapy experience an appropriate device shock by the second year after implant. Table 3 displays the odds ratios for those factors associated with the risk of receiving an appropriate shock. Therapy with the neurohormonal antagonists including $\beta$-blockers, angiotensin-converting enzyme, angiotensin receptor blocker agents, and female gender reduced the risk of a shock. Class IV versus class III HF status increased risk.

Impact of ICD Shocks on Outcome
Unadjusted risk of death or first all-cause hospitalization (Figure 2A; HR, 1.6; P=0.009), pump failure death or hospitalization (Figure 2B; HR, 2.4; P=0.001), sudden death mortality (Figure 2C; HR, 3.0; P=0.03), and total mortality (Figure 2D; HR, 1.7; P=0.03) were increased by the need for an appropriate shock. After adjusting for the prespecified variables, including class IV HF and LVEF, mortality was the only end point not increased by shock therapy (HR, 1.3; P=0.28).

Number Needed to Treat to Prevent Sudden Death
Table 4 provides data on the number of patients needed to treat to prevent 1 patient from reaching the COMPANION primary and secondary (mortality) study end points as well as HF death, hospitalization, and sudden cardiac death. For sudden death prevention, 25 patients would need to receive a CRT-D device for 1 patient to receive survival benefit from sudden death over a 15-month period after device implant. The numbers needed to treat are significantly reduced when

<table>
<thead>
<tr>
<th>Table 2. Risk of Sudden Cardiac Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>CRT-D</td>
</tr>
<tr>
<td>CRT</td>
</tr>
<tr>
<td>LVEF $\geq 20%$</td>
</tr>
<tr>
<td>QRS $\geq 160$ ms</td>
</tr>
<tr>
<td>Female gender</td>
</tr>
<tr>
<td>NYHA class IV</td>
</tr>
<tr>
<td>Renal dysfunction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3. Risk of Appropriate Shock Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>$\beta$-Blocker use</td>
</tr>
<tr>
<td>ACE inhibitor use</td>
</tr>
<tr>
<td>Angiotensin receptor blocker use</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>HF functional class IV</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme.

*Odds ratio for appropriate shock vs no shock/inappropriate only shock.
evaluating the primary, secondary, and HF composite end points.

**Discussion**

**Sudden Death Risk**

The present study demonstrates that cardiac resynchronization therapy combined with an ICD favorably impacts sudden death risk. Although the COMPANION Trial was not designed to compare CRT therapy with CRT-D therapy, the findings of the present study demonstrate a positive therapeutic association with CRT-D but not CRT therapy with regard to sudden death risk reduction.\(^1,2\)

In the Cardiac Resynchronization-Heart Failure (CARE-HF) study of 813 patients, which compared medical therapy to a CRT device alone, total mortality was reduced by 36% at 29 months with a CRT device\(^10\) (\(P<0.002\)). When follow-up was extended to 36 months, risk of death due to HF (\(P=0.003\)) and sudden death (\(P=0.006\)) were both reduced.\(^10,11\) Although sudden death risk was decreased in CARE-HF with CRT alone, it required 36 months of follow-up to demonstrate, and sudden death still accounted for 32% of all deaths in CRT-treated patients. In COMPANION, sudden death accounted for 28% of OPT deaths, 37% of CRT deaths, and 17% of deaths in CRT-D treated patients.

These data from CARE-HF and COMPANION suggest that when HF is advanced enough to merit CRT therapy, CRT-mediated improvement in HF status is an appropriate therapeutic target for sudden death prevention in many but not all subjects. CRT-associated improvements in HF severity may indirectly result in fewer sudden deaths as a result of reductions in potentially proarrhythmic electrolyte shifts, HF-induced worsening of cardiac ischemia, or proarrhythmic neurohormonal activation.\(^3,13\) The finding that QRS duration \(>160\) ms reduced sudden death risk may suggest that these subjects, by virtue of having more QRS delay, received greater benefit from CRT and sudden death risk were related to improved HF status.\(^14\) Conversely, subjects with longer QRS duration may be at greater risk of HF progression, even with CRT. Time-dependent prevention of, or reversal of, structural and electrical remodeling may also lessen the risk of malignant arrhythmia.\(^15-17\) There does not appear to be a direct beneficial effect of CRT on the arrhythmia substrate early after implantation of a CRT device. In a retrospective analysis of data from the Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD) trial of CRT-D therapy in patients with primary and secondary ICD indications, there was no difference in ICD VT or VF detections between patients randomized to CRT therapy on or CRT therapy off in the first 6 months after device implantation.\(^6\)

Our finding that LVEF \(>20\)% reduced sudden death risk and that class IV HF increased risk is consistent with observations that, although HF is the predominant mode of cardiovascular death in the setting of more advanced HF, the absolute risk of sudden death increases with disease severity.\(^2,18\)
ICD Therapy in CRT-Treated Patients: A Marker of Disease Severity?

The percentage of CRT-D–treated patients who experienced appropriate ICD shocks in COMPANION and had class III or IV HF is twice that reported for primary prevention right ventricular ICD-treated patients with predominantly class II HF. Our observation that the risk of shock exceeds the risk of sudden death in OPT-treated patients implies that not all shocks will result in a fatal event. Nonetheless, even if the sustained ventricular arrhythmia would have terminated spontaneously prior to shock therapy, it is reasonable to assume that it may have introduced morbidity such as syncope or worsening of HF.

In the second Multicenter Automatic Defibrillator Implantation Trial (MADIT-II) of ICD therapy in postinfarction patients with left ventricular dysfunction, women had less ICD therapy for VF but equivalent VT therapies and mortality benefit. The total number of women enrolled in both COMPANION and MADIT-II may be too few to make any firm conclusions, but the COMPANION data also show that women benefit similarly for the primary end point analysis but receive less ICD therapy for VT or VF.

Perhaps the most provocative and concerning finding of the COMPANION ICD therapy data is the need for ICD therapy in CRT-treated patients predicts a number of major adverse outcomes, including risk of subsequent sudden death. The finding of a protective effect of the neurohormonal antagonists such as β-blockers, angiotensin-converting enzyme, and angiotensin receptor blocker inhibitors on the risk of ICD shock but not necessarily sudden death is not surprising, as therapy with these agents was protocol-mandated and sudden deaths are not always necessarily due to arrhythmias. Although prior COMPANION analysis did show that CRT-D mortality benefit was due to a reduction in sudden death, not all ICD shocks will prevent sudden death, particularly if it results from nontachyarrhythmic mechanisms such as pulmonary or systemic embolization or electrical-mechanical dissociation. The onset of a sustained ventricular arrhythmia in this patient population may represent a marker of worsening disease status. HF symptom severity was linked to ICD shock rate in a prospective study that evaluated the incidence and factors associated with right ventricular ICD therapy in a mixed group of ICD recipients. The risk of a device therapy increased 2-fold for patients with class III HF symptoms compared with class I or II. This interrelationship between HF severity and sudden death risk was observed to be bidirectional in the primary prevention MADIT II ICD trial. In patients that experienced appropriate ICD shock therapies, the risk of a HF exacerbation was nearly doubled over the next year. At the very least, an appropriate ICD shock in our CRT-D treated patients interrupted a sustained arrhythmia that may have introduced morbidity in terms of worsening symptoms, prevention of syncope, injury, or death. Yet our data also indicate that overall risk does not end after appropriate and effective therapy delivery. In fact, the increased subsequent risks of HF hospitalizations and death suggest these HF patients may benefit from closer clinical surveillance or additional adjunctive therapies to help further mitigate these risks.

Of clinical importance, the number needed to treat analysis favors the placement of the ICD with CRT therapy in COMPANION patients. This is supported by a similar analysis performed for the RV ICD for primary prevention of sudden death that defined a number needed to treat threshold for a clinically meaningful survival benefit with ICD therapy of 50 patients to prevent 1 death of any cause. That analysis assumed a sudden death risk of 3% per year, much lower than the 5.8% death risk observed in the medically treated COMPANION arm.

**Study Limitations**

Although study hypotheses were determined before data analysis, this was a post hoc analysis of COMPANION data. Appropriate ICD shock is not a surrogate for mortality, as sustained VT/VF may terminate spontaneously before shock delivery or may occur in conjunction with a terminal event such as fatal pulmonary embolism. Conclusions derived from the composite mortality and hospitalization end points must
be considered with caution, as all follow-up times and events prior to appropriate shock were excluded from the “Appropriate Shock” arm, making the reasons for any differences in arms challenging to isolate. ICD electrograms were not available for central adjudication of appropriate or inappropriate shocks; such adjudication occurred at the implant centers. Detection and ICD therapy programming was not mandated. This limited our analysis of the prognostic importance of shocks for VT versus VF. The presence of renal dysfunction was not rigorously defined in the COMPANION protocol, limiting interpretation of risk-associated sudden death. Previous studies have linked arrhythmia risk to chronic renal dysfunction in populations with and without ICDs. Chronic renal dysfunction is associated with a heightened susceptibility to sudden death and elevated defibrillation thresholds.23,24

Conclusions

In CRT candidates, sudden cardiac death risk is associated with higher NYHA class and renal dysfunction. In primary prevention CRT-D recipients, reduction in the risk of an appropriate shock is associated with medical therapy with neurohormonal antagonists and female gender, whereas NYHA functional class IV clinical status increased risk. Compared with the risks in patients not experiencing ICD shocks, shock therapy is associated with increased risk of hospitalization and death from both sudden and pump-failure causes.

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Disclosures

Dr Saxon has received honoraria from, served as a consultant to and on the advisory board for, and received a research grant for work on MADIT-CRT and CONTAK Renewal 3 AVT from Guidant Corporation. Dr Saxon has also received honoraria, grants, and consulting fees from Medtronic. Dr Bristow has served as a consultant and on the advisory board for Guidant Corporation. Dr Boehmer has received research grants from Guidant Corporation and Medtronic, Inc, and honoraria from Guidant Corporation and has served as a consultant on the Guidant Heart Failure Advisory Board. Dr Kass has received honoraria from, served as a consultant to, and served on the Heart Failure, Neurostimulation, and Biologicals advisory boards of Guidant Corporation. He has also received research grants for work on BICAF, CRT in Patients, and Molecular Signaling in Mice. Drs De Marco, Carson, and Feldman have served as consultants and on the Advisory Board for Guidant Corporation. Dr DiCarlo is the Senior Director of Cardiovascular Development, Pfizer Global Research and Development, with ownership interest in Pfizer, Inc. E. Galle and F. Ecklund have ownership interest in Guidant Corporation. Dr Krueger reports no conflicts.

References


**CLINICAL PERSPECTIVE**

The vast majority of implantable cardioverter defibrillators (ICDs) are implanted for primary prevention of sudden death. Cardiac resynchronization therapy (CRT) in conjunction with an ICD represents nearly one third of all ICDs implanted in the United States and offers the potential benefit of improving HF for patients with class III or IV symptoms and ventricular dyssynchrony. Although CRT can be implemented with pacing, without defibrillation, 90% of patients receive CRT-defibrillator. The predictors of sudden death and appropriate shock in the COMPANION Trial evaluates sudden death and appropriate shock outcomes in patients treated with CRT devices versus medical therapy. Sudden death risk paralleled HF severity and was associated with class IV HF and renal dysfunction. Women and patients with better LVEFs were at lower risk. Appropriate ICD shocks for ventricular arrhythmias occurred at a rate of 15% at 16 months, greater than in primary prevention ICD studies without CRT, and much greater than the risk of sudden death without an ICD, which suggests that not all appropriate shocks would have resulted in sudden death. Appropriate shocks are associated with worse subsequent outcome, including the combined end point of all-cause hospitalization and mortality. These findings are both reassuring and concerning when viewed in the context of our clinical practice. The CRT-defibrillator device reduces sudden death compared with medical therapy, but ventricular arrhythmias are a marker for worse outcomes despite effective termination by the device, which suggests that additional evaluation and therapies should be considered for these high-risk patients.
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