Ventricular tachycardia or ventricular fibrillation occurs less often in patients with left bundle branch block and combined resynchronization and defibrillators than in patients with narrow QRS and conventional defibrillators

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Aims
Mortality in chronic heart failure (CHF) patients with left bundle branch block (LBBB) is high. Cardiac resynchronization therapy (CRT) reduces symptoms and mortality in CHF patients with LBBB. Whether CRT promotes or prevents ventricular tachycardia (VT)/ventricular fibrillation (VF) remains controversial, however. Therefore, we aimed to analyse arrhythmia-related CRT effects and characterized the VT/VF incidence in CRT-defibrillator patients and matched controls with conventional implantable cardioverter-defibrillators (ICDs) for primary prevention of sudden cardiac death.

Methods and results
We enrolled 134 patients [110 men, left ventricular ejection fraction (LVEF) 24 ± 8%, 71 coronary artery disease, CRT–ICD 67, conventional ICD matched controls 67, follow-up 31 ± 17 months] and monitored overall survival and the time to a first VT/VF episode. Controls did not have LBBB. They were otherwise matched for age, LVEF, and follow-up duration. Gender and underlying disease did not differ between the groups. Kaplan–Meier analysis revealed more favourable arrhythmia-free survival in CRT–ICD vs. conventional ICD patients [hazard ratio (HR) 2.26, confidence interval (CI) 1.09–4.67, log rank $P = 0.023$]. The difference persisted in the multivariate Cox regression analysis (HR 3.25, CI 1.18–8.93, $P = 0.022$). Overall survival was similar in both groups (HR 1.45, CI 0.55–3.82, $P = 0.45$).

Conclusions
Chronic heart failure patients with LBBB treated with CRT–ICD, experience less and delayed VT/VF episodes compared with matched controls without LBBB receiving conventional ICD. In the long-term, CRT appears to exert antiarrhythmic effects and to attenuate the particularly high arrhythmia-related risk of CHF patients with LBBB. The incremental benefit of adding the ICD option to CRT pacing in LBBB patients appears questionable.

Keywords
Cardiac resynchronization therapy • Implantable cardioverter-defibrillator • Ventricular tachycardia • Ventricular fibrillation • Left bundle branch block • Sudden cardiac death

Introduction
Left bundle branch block (LBBB) causes cardiac electromechanical dyssynchrony.\textsuperscript{1} Subsequently, chronic heart failure (CHF) patients with LBBB deteriorate more quickly than CHF patients without a wide-QRS complex.\textsuperscript{2} As a matter of fact, any intraventricular conduction delay predicts poor overall survival in CHF patients.\textsuperscript{3,4} A subanalysis of the Sudden Cardiac Death in Heart Failure...
Depressed systolic LV function. So far, the data on CRT-related structure, CHF symptoms, and survival in patients with LBBB and risk. Cardiac resynchronization therapy (CRT) improves the LV status, but also accentuates the CHF-associated arrhythmia-related risk. Cardiac resynchronization therapy (CRT) improves the LV structure, CHF symptoms, and survival in patients with LBBB and depressed systolic LV function. So far, the data on CRT-related effects on the occurrence of ventricular arrhythmias [ventricular tachycardia (VT)/ventricular fibrillation (VF)] are inconsistent. Therefore, we compared the incidence of VT/VF in a CRT–ICD-treated cohort with LBBB vs. matched CHF control patients without LBBB, who were solely treated with a conventional ICD.

Methods

Implantation procedure and selection of study patients

After having obtained written informed consent, the implantations were carried out in the catheterization laboratory under local anaesthesia and deep sedation only during defibrillation threshold testing. The defibrillation leads were placed within the right ventricular apex. Manufacturers of the implanted devices included Biosense Webster, Guidant Corp., and Medtronic Inc. All ICDs were equipped with electrogram-based storage capabilities for VT/VF episodes.

We studied 134 patients with systolic CHF, who were candidates for primary prevention ICD treatment according to current guidelines. The CRT–ICD cohort consisted of 67 consecutive CHF patients with LBBB. Control patients without LBBB were identified out of a prospectively characterized ICD cohort and matched by pairs with respect to the baseline LVEF, follow-up duration, and age.

Antibradycardia settings

A common objective of conventional single- and dual-chamber ICD antibradycardia settings was to achieve a preferably low ventricular pacing percentage. In single-chamber devices a low ventricular rate (35–50 bpm) along with the VVI mode was programmed. In dual-chamber ICD the atrio-ventricular (AV) delay was prolonged, until ventricular pacing ceased. In patients with normal AV conduction (i.e. PR interval ≤200 ms), manual AV delay prolongation was accomplished by disabling of tracking in the DDI(R) mode. Cardiac resynchronization therapy–ICD devices were set to the DDD mode at a lower rate of 50 bpm except where sinus node dysfunction was present. In patients with sinus bradycardia, the DDD(R) mode was chosen along with a lower rate of 60–70 bpm. Cardiac resynchronization therapy–ICD systems were optimized guided by Doppler and tissue Doppler echocardiography within 2 weeks following the implantation.

Antitachycardia settings

Since all patients had a primary prevention ICD indication, the antitachycardia settings could not be oriented at an index arrhythmia, but had to be empiric. Usually, two tachycardia detection zones were programmed. A VT zone was defined >170–180 bpm and a VF zone was set beyond 200 bpm. Ventricular tachycardia detection was based on device-specific discrimination algorithms in order to increase diagnostic specificity. Treatment for VT included burst and ramp antitachycardia pacing (ATP) with subsequent shocks in case of need. Tachyarrhythmias that were detected within the VF zone were treated by shocks.

Follow-up

We followed the patients every 3–4 months. Additional unscheduled device interrogations were performed in case of symptomatic episodes and/or shock delivery. The episode electrograms and arrhythmia log were printed at each follow-up. Ventricular tachycardia VF episodes were analysed and validated by three experienced examiners. Based on the ICD marker channels and stored electrograms, the detections and interventions of the device were classified as appropriate or inappropriate. The time from implantation to a first appropriate treatment episode was recorded. In-hospital deaths were ascertained and relatives and/or family physicians were contacted in case the patients did not present for a scheduled routine follow-up. The time interval between implantation and death was recorded. QRS intervals were obtained from unpaced standard 12-lead surface electrocardiogram (ECG) at the time of implantation. The ECGs were recorded at a horizontal speed of 50 mm/s and a magnification of 10 mm/mV with a digital sampling rate of 1000 Hz using a computer-based system (Siemens MegaCart). The measurements were printed according to the built-in software. The CHF medication was documented at the time of hospital discharge after ICD implantation. Outcome measurements of the study included survival free from death or VT/VF episodes, and overall survival.

Statistics

Categorical variables are reported as absolute numbers and percentages. Continuous variables are presented as means ± standard deviation, as long as they appeared to be normally distributed. Non-normally distributed data are given as medians and interquartile range. Normal distribution was tested applying the Kolmogorov-Smirnov method. Unpaired Student’s t-test and Fisher’s exact test were used for horizontal comparisons as appropriate. Kaplan–Meier and multivariate Cox regression analyses were used to examine survival without a first appropriate ICD treatment episode and overall survival. Baseline parameters with significant differences between the study groups were included as covariates into the multivariate analyses.

Results

Characteristics of the study groups

Demographic data of the CRT–ICD and conventional ICD study groups are outlined in Table 1. Most of the CHF patients were men. The study groups did not differ with respect to LVEF, age.
During long-term follow-up (31 months for all patients), 5 of 67 (7.5%) CRT–ICD patients, and 14 of 67 (20.9%) patients of the ICD group patients developed VT/VF after an average arrhythmia-free interval of 13 months. This difference was statistically significant (P = 0.026). Ventricular tachycardia was detected in 4 patients, whereas 15 patients had their first episode classified as VF by the device. Kaplan–Meier analysis revealed significantly more favourable arrhythmia-free survival of CRT–ICD patients compared with the conventional ICD group [log rank P = 0.023, hazard ratio (HR) 2.26, 95% confidence interval (CI) 1.09–4.67].

The advantage for the CRT–ICD group (Figure 1) persisted also in the multivariate Cox regression analysis (HR 3.25, 95% CI 1.18–8.93, P = 0.022). Angiotensin-converting enzyme inhibitor/ARB treatment and QRS duration did not confound the results. In seven patients, the episode validation revealed inappropriate anti-tachycardia treatment episodes. The occurrences of inappropriate treatment episodes (shock or ATP) were not significantly different between CRT–ICD (5.9%) and conventional ICD (4.5%) patients. Missing beta-blocker therapy was associated with a higher incidence of appropriate VT/VF incidence (HR 2.97, 95% CI 1.03–8.52, P = 0.04).

**Long-term all-cause mortality**

During long-term follow-up, 17 of 134 patients (12.7%) died, which corresponds to a 4.9% yearly mortality rate. The cumulative

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**Table 1 Characteristics of the study groups**

<table>
<thead>
<tr>
<th>CRT–ICD</th>
<th>Matched controls with conventional ICD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 67</td>
<td>n = 67</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>63 ± 9</td>
<td>62 ± 9</td>
</tr>
<tr>
<td>Men (n%)</td>
<td>53/79</td>
<td>57/85</td>
</tr>
<tr>
<td>Coronary artery disease (n%)</td>
<td>32/48</td>
<td>39/58</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>23 ± 7</td>
<td>25 ± 8</td>
</tr>
<tr>
<td>History of atrial fibrillation (n%)</td>
<td>8/12</td>
<td>13/19</td>
</tr>
<tr>
<td>QRS width (ms)</td>
<td>160 ± 28</td>
<td>118 ± 23</td>
</tr>
<tr>
<td>PR interval (ms)</td>
<td>189 ± 48</td>
<td>183 ± 32</td>
</tr>
<tr>
<td>Beta-blocker (n%)</td>
<td>64/96</td>
<td>62/93</td>
</tr>
<tr>
<td>Amiodarone (n%)</td>
<td>15/22</td>
<td>9/13</td>
</tr>
<tr>
<td>Glycosides (n%)</td>
<td>17/25</td>
<td>16/24</td>
</tr>
<tr>
<td>ACE inhibitors or ARB (n%)</td>
<td>61/91</td>
<td>67/100</td>
</tr>
<tr>
<td>Spironolactone/ eplerenone (n%)</td>
<td>50/75</td>
<td>49/73</td>
</tr>
<tr>
<td>Diuretics (n%)</td>
<td>58/87</td>
<td>57/85</td>
</tr>
<tr>
<td>Follow-up duration (months)</td>
<td>32 ± 17</td>
<td>31 ± 18</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator.
mortality amounted to 10.4% in the CRT–ICD group and to 14.9% in the conventional ICD group. The difference was not statistically significant (HR 1.45, 95% CI 0.55–3.82, P = 0.45). By multiple variable regression analysis, after correction for significantly different baseline parameters (ACE inhibitor/ARB treatment and QRS duration), mortality remained similar in both study groups (HR 2.31, 95% CI 0.56–9.54, P = 0.25, Figure 2).

Discussion

We found that survival free from a first VT/VF episode appeared to be more favourable in CRT–ICD patients compared with that in the case of matched HF control patients with conventional ICD. We believe these data are remarkable, since LBBB is a VT/VF risk factor. The control group should have done better on account of their narrow QRS complexes. In that regard, they did not need CRT. Furthermore, their VT/VF risk was reduced on account of a narrow QRS. Nonetheless, we found that LBBB patients with CRT-defibrillators do even better than their non-LBBB counterparts, as long as they are treated with this device. The chance of experiencing a potentially life-threatening VT/VF is decreased by CRT to a level, which is even lower than in CHF patients without LBBB. This state-of-affairs is most likely due to the markedly favourable reverse LV remodelling which is provoked by CRT in LBBB patients.7 However, our results do not contradict pathophysiological considerations and anecdotal clinical reports relating to possible proarrhythmic effects of LV-based pacing in individual patients.

Previous studies

Several factors including scar formation or regional fibrosis, myocardial ischaemia, symptomatic heart failure,15 changing ionic currents, delayed or early after-depolarization, abnormal calcium handling, enhanced automaticity, and sympathetic activation16,17 all favour the incidence of VT/VF. Delayed intraventricular conduction enhances the risk of CHF patients to die suddenly or to sustain life-threatening ventricular tachyarrhythmias.18,19. The reason for the association of LBBB and ventricular arrhythmias is not completely understood. Indeed, inhomogeneous ventricular conduction can be hypothesized to create irregular refractoriness and to thereby promote re-entrant electrical activation and the development of malignant ventricular tachyarrhythmias. In addition, electromechanical dyssynchrony impairs LV efficiency4 and increases neurohumoral activation, which also favours the development of VT/VF.20 Thus, CRT can be expected to lower the arrhythmia-related risk while producing more uniform ventricular activation and alleviating the autonomous dysbalance.21 Extended long-term follow-up data from one randomized trial on CRT22 have in fact demonstrated not only mortality from LV pump failure, but also sudden mortality to be reduced through biventricular pacing compared with a no-pacing period.8 Moreover, CRT has been reported to decrease the inducibility of VT.9 One registry analysis reported the volume responder status to predict the frequency of ventricular ectopic beats and a borderline significant reduction of VT/VF episodes.23 Similar results have been reported from another typical CRT cohort,24 whereas recently the effect was not confirmed in patients with LBBB and mild CHF.25 On the other hand, CRT has been conjectured to increase the risk for VT,10 since pacing the LV from the epicardium through coronary sinus branches has been shown to produce transmural dispersion of ventricular activation and to prolong ventricular repolarization.11 In order to examine the hypothesis that CRT could increase the occurrence of VT/VF, one retrospective study analysed pooled data from two randomized trials and found no significant interaction between CRT and ventricular arrhythmias.26 Another study on proarrhythmic effects of CRT reported 5 of 145 consecutive patients who experienced VT or VF storming early after the upgrade of an ICD system to a CRT device.13 Hence, justifiable information is available as well to establish antiarrhythmic virtues as also to apprehend proarrhythmic mechanisms by CRT. Our data suggest that all in all antiarrhythmic effects through CRT predominate.

Study population

We included consecutive CRT–ICD patients and matched controls with conventional ICD. With respect to baseline characteristics (age, gender, LVEF, underlying heart disease, history of atrial fibrillation, and QRS duration) the CRT–ICD subgroup represents a typical CRT cohort.7,27 In contrast, HF control patients
with conventional defibrillators corresponded less to a typical primary prevention ICD cohort, since through matching by pairs this cohort has a distinctly lower LVEF and is slightly older than patients from current ICD registries. The conventional ICD study group probably had more advanced structural heart disease compared with standard unselected primary prevention defibrillator patients.\textsuperscript{18,28}

### Incidence of ventricular tachycardia or ventricular fibrillation events

Control group patients received earlier and more frequent appropriate ICD therapy for VT or VF than CRT–ICD patients. The incidence of VT/VF among control patients was comparable with that reported by the Sudden Cardiac death in Heart Failure (SCD-HeFT) in 2005,\textsuperscript{5} but was clearly higher than published from current patient series.\textsuperscript{28} Left ventricular ejection fraction is a well-known predictor of VT/VF episodes.\textsuperscript{19} The impact of the LV systolic function may explain the differing VT/VF incidence, since control group patients of this study had lower LVEF than unselected primary prevention ICD patients. This is also in line with the data on the association of VT/VF episodes and favourable LV remodelling in patients with advanced HF.\textsuperscript{24} Apart from being treated with a conventional ICD, missing beta-blocker treatment was the only predictor of VT/VF episodes in the collective population of this study. This situation may be due to the lacking beta-receptor blocking effect and enhanced beta-adrenergic activity. A second possible reason for this association is a selection effect due to the particularly bad overall condition of patients who cannot tolerate beta-blockers.

### Long-term overall survival

Less people died in the collective study population (4.9%/year), when compared with the ICD-treated subgroups of the SCD-HeFT (5.8%/year)\textsuperscript{5} and MADIT II (8.5%/year)\textsuperscript{6} primary prevention ICD trials, although the extent of LV compromise appeared similar (mean LVEF in MADIT II and SCD-HeFT 24% as in the present study). This may be explained by state-of-the-art concomitant medical therapy and in particular by the higher use of beta-blockers which was only \textasciitilde{}70% in MADIT II and SCD-HeFT in relation to 94% in the present study. The overall survival was similar in the CRT–ICD group (4.0%/year) vs. the conventional ICD group (5.8%/year), although from the outset HF patients with LBBB should particularly be exposed to pump failure and arrhythmic death. This supports the hypothesis that functional and structural improvement through CRT is able to compensate for the excess mortality risk, which is associated with LBBB in HF patients.

### Clinical implications

Although this study is not suited to derive decisive clinical conclusions, our results give rise the question of incremental benefit of adding the defibrillator option to biventricular pacing in LBBB patients with advanced CHF. Nevertheless, during a first CRT device implantation, in our opinion the defibrillator option in biventricular pacing CRT devices should not be abandoned for two reasons. First, the antiarrhythmic effectiveness of CRT appears to depend on structural LV improvement,\textsuperscript{24,25} which cannot be achieved in all patients.\textsuperscript{29} Left ventricular structural improvement and the evolution of the arrhythmia-related risk cannot be anticipated with certainty at the time of implantation. Moreover, specific topic electrophysiological properties in some individual patients may be suited to promote VT/VF during LV-based pacing. This subset of high-risk patients cannot be identified with certainty from the outset and could also require antidysrhythmia protection. But downgrade to a pure CRT pacing device might be considered during pulse generator exchange in patients with clearly demonstrated reverse LV remodelling and absent VT/VF during the first generator’s lifecycle. In this patient subpopulation, the discernibly low residual risk to experience life-threatening VT/VF might no longer justify to accept unwanted side effects of ICD treatment (e.g. inappropriate shocks).

### Study limitations

We are aware of limitations. The number of enrolled patients is relatively low. Therefore, by design the study was not suited to detect minor differences in overall survival. We matched our subjects in terms of LVEF, age, and follow-up duration. Many additional parameters did not differ between the groups and multiple variable analyses accounted for differing parameters. Nonetheless, we cannot be certain to have controlled all potential confounders that influence the incidence of VT in CHF.

### Conclusions

Chronic heart failure patients with LBBB treated with CRT–ICD, experience less and delayed VT/VF episodes compared with matched controls without LBBB receiving conventional ICD. In the long-term CRT appears to exert antibradyarrhythmic effects and to attenuate the particularly high arrhythmia-related risk of CHF patients with LBBB. The incremental benefit of adding the ICD option to CRT pacing in LBBB patients appears questionable. Clinical implications should be corroborated by larger studies. They might include abandoning the ICD option in generator exchanges after a successful first CRT device lifecycle.

### Conflict of interest

M.S. receives research grants and speaker’s honoraria from Biotronik, Boston Scientific, Medtronic, and Sorin Group.

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### References


