Cardiac resynchronization therapy (CRT) is an established treatment for patients with heart failure (HF), low ejection fraction, and a wide QRS, improving clinical outcome. Recent substudy analysis from the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) trial showed that the benefit from CRT was evident in patients with left bundle branch block (LBBB) but not in those with non-LBBB.

It has also been shown that in patients with HF, a prolonged PR interval is associated with unfavorable clinical outcome, and there is a benefit from shortening atrioventricular (AV) conduction delay in CRT patients. We hypothesized that this effect is more relevant in patients with non-LBBB and may identify responders to CRT with defibrillator (CRT-D).

The effects of CRT-D therapy on clinical outcome in non-LBBB patients (including right bundle branch block [RBBB] and intraventricular conduction delay [IVCD]) stratified by the baseline PR interval have not yet been evaluated.

Background—In Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT), patients with non–left bundle branch block (LBBB; including right bundle branch block, intraventricular conduction delay) did not have clinical benefit from cardiac resynchronization therapy with defibrillator (CRT-D). We hypothesized that baseline PR interval modulates clinical response to CRT-D therapy in patients with non-LBBB.

Methods and Results—Non-LBBB patients (n=537; 30%) were divided into 2 groups based on their baseline PR interval as normal (including minimally prolonged) PR (PR <230 ms) and prolonged PR (PR ≥230 ms). The primary end point was heart failure or death. Separate secondary end points included heart failure events and all-cause mortality. Cox proportional hazards regression models were used to compare risk of end point events by CRT-D to implantable cardioverter defibrillator therapy in the PR subgroups. There were 96 patients (22%) with a prolonged PR and 438 patients (78%) with a normal PR interval. In non-LBBB patients with a prolonged PR interval, CRT-D treatment was associated with a 73% reduction in the risk of heart failure/death (hazard ratio, 0.27; 95% confidence interval, 0.13–0.57; P<0.001) and 81% decrease in the risk of all-cause mortality (hazard ratio, 0.19; 95% confidence interval, 0.13–0.57; P<0.001) compared with implantable cardioverter defibrillator therapy. In non-LBBB patients with normal PR, CRT-D therapy was associated with a trend toward an increased risk of heart failure/death (hazard ratio, 1.45; 95% confidence interval, 0.96–2.19; P=0.078; interaction P<0.001) and a more than 2-fold higher mortality (hazard ratio, 2.14; 95% confidence interval, 1.12–4.09; P=0.022; interaction P<0.001) compared with implantable cardioverter defibrillator therapy.

Conclusions—The data support the use of CRT-D in MADIT-CRT non-LBBB patients with a prolonged PR interval. In non-LBBB patients with a normal PR interval, implantation of a CRT-D may be deleterious.

Clinical Trial Registration—http://clinicaltrials.gov; Unique Identifier: NCT00180271.
Therefore, the aim of the present study was (1) to investigate the effect of baseline PR interval on clinical outcome in patients with non-LBBB, and (2) to assess clinical response to CRT-D versus implantable cardioverter-defibrillator (ICD) therapy in patients with non-LBBB and normal or prolonged PR interval at baseline.

Methods

Study Population
The design, protocol, and results of the MADIT-CRT study have been published previously. In short, 1820 patients with ischemic cardiomyopathy (New York Heart Association functional class I or II) or nonischemic cardiomyopathy (New York Heart Association functional class II only), left ventricular (LV) EF <30%, and a wide QRS with a duration ≥130 ms were randomized to receive CRT-D or ICD therapy in a 3:2 ratio. All eligible patients met the guideline criteria for ICD. Patients were excluded as described previously.

There were 537 patients (30%) with a non-LBBB ECG pattern (including RBBB or IVCD), enrolled in MADIT-CRT. We excluded patients from the present analysis if their baseline PR interval measurement was not available (n=3). Accordingly, the present study sample comprised 534 (99%) of the 537 patients with non-LBBB enrolled in MADIT-CRT, 327 (61%) of them randomized to CRT-D and 207 (39%) to ICD-only therapy. The analyses were performed on an intention-to-treat basis.

Device Implantation and Programming
Generally available transvenous single- or dual-chamber ICD and CRT-D devices (Boston Scientific) were implanted according to standard methods. In patients with an implanted CRT-D, maximum biventricular pacing was recommended, with an AV delay programmed using a proprietary optimization algorithm called ExpertEase for Heart Failure dependent on baseline PR interval and QRS duration.

Data Acquisition and Patient Follow-Up
The MADIT-CRT trial was performed from December 22, 2004, through June 22, 2009, with extended follow-up until September 10, 2010. After the device implantation, patients had an ambulatory Holter ECG at enrollment. Dr Wojciech Zareba). The P-wave duration was measured on the enrollment ECGs between 25 mm/s speed in the Electrocardiography Core Laboratory (PI:

Definitions and End Points
Intraventricular conduction disturbances (LBBB, RBBB, IVCD) were defined according to criteria approved by the World Health Organization, as described in our previous publication. Non-LBBB ECG pattern included those with RBBB or IVCD.

PR interval was manually measured on the enrollment ECGs before device implantation on the resting 12-lead surface ECG recorded with 25 mm/s speed in the Electrocardiography Core Laboratory (PI: Dr Wojciech Zareba). The P-wave duration was measured on the Holter ECG at enrollment.

Patients with non-LBBB ECG pattern were divided into 2 prespecified groups based on their baseline PR interval: PR <230 ms (normal PR group, with a mean PR interval value of 254 ms and range of 230–360 ms), and 438 non-LBBB patients (78%) comprised the normal PR group (with a PR interval <230 ms), including those with minimally prolonged PR intervals. Clinical characteristics of non-LBBB patients stratified by baseline PR interval are depicted in Table 1. Patients with a prolonged PR were sicker, were older, less often women, had more often prior coronary artery bypass graft, and atrial arrhythmias before enrollment (Table 1). CRT-D treatment was equally distributed between the PR interval patient groups (63% versus 61%; P=0.779). Patients with long PR had longer P waves than patients with a normal PR interval (153.1±20.3 versus142.2±16.6; P<0.05).

Risk of Cardiac Events by Baseline PR Interval
The risk of cardiac events was evaluated in patients with an implanted ICD-only (n=207; 39% of the total non-LBBB cohort). During the mean follow-up of 29.4±11 months, the primary end point of HF or death was met in 38 of 171 patients (22%) with a normal PR and in 17 of 36 (42%) patients with a prolonged PR; 14 of 171 ICD patients (8%) died with a normal PR compared with 8 of 36 patients (22%) with a prolonged PR interval.

Patients with prolonged PR interval had significantly higher incidence of HF/death (P<0.001), HF only, (P<0.001), and death (P=0.003; Figure 1) corresponding to a >3-fold increase in the risk of HF/death, HF only, and death in the multivariable models compared with the normal PR interval group (Table 2).

Response to CRT-D in Patients With Non-LBBB and a Prolonged PR Interval
In non-LBBB patients with prolonged PR interval and an implanted CRT-D, there was a significantly lower crude event
rate of HF/death (15/60 patients [25%]) compared with those with an implanted ICD-only (17/36 patients [47%]).

In patients with non-LBBB and a prolonged PR interval, there was a significant reduction in the cumulative probability of HF/death by CRT-D compared with ICD-only (P=0.015; Figure 2A). This effect was translated to a 73% risk reduction in HF/death in CRT-D patients with a prolonged PR interval (PR ≥230 ms) at baseline compared with ICD-only (P<0.001; Table 3). This was consistent for HF only (P<0.001) (Table 3).

Notably, in non-LBBB patients with prolonged PR interval, CRT-D was associated with a borderline significant reduction in the cumulative probability of all-cause mortality (P=0.059; Figure 2B), which became significant in the multivariable model with an 81% risk reduction (P<0.001; Table 3) compared with ICD-only.

### Figure 1.
Kaplan–Meier cumulative probability of (A) heart failure (HF)/death, (B) HF only, and (C) all-cause mortality in implantable cardioverter defibrillator patients with non–left bundle branch block by baseline PR interval.

**Response to CRT-D in Patients With Non-LBBB and a Normal PR Interval at Baseline**

On the contrary, patients with a normal PR interval had a trend toward an increased incidence of HF/death with an implanted CRT-D (P=0.065) compared with ICD (Figure 2C), corresponding to a borderline 45% increase in the risk of HF/death (P=0.078). A significant bidirectional interaction was observed in the CRT-D to ICD effect on HF/death between patients with a normal versus a prolonged PR interval (interaction P<0.001).

In the normal PR group, there were 58 deaths in total (12%), 14 (3%) in the ICD treatment arm and 44 (10%) in the CRT-D arm. In the CRT-D arm with a normal PR interval, 22 patients died of cardiac causes (17 HF, 2 arrhythmic deaths, and 3 other cardiac death), 17 patients died of noncardiac cause, and 5 of unknown origin.
CRT-D patients with non-LBBB and a normal PR interval had significantly higher incidence of all-cause mortality \((P=0.021)\) compared with ICD-only patients (Figure 3D), with a >2-fold increase in the risk of death (hazard ratio, 2.14; 95% confidence interval, 1.12–4.09; \(P=0.022\)). Again, there was a significant bidirectional treatment interaction between patients with a normal versus a prolonged PR (interaction \(P<0.001\)).

### Risk of Events and Response to CRT-D in Non-LBBB by Quintiles of PR Interval

We assessed the effect of baseline PR interval on HF or death using quintiles in ICD patients with non-LBBB. As shown in Figure 3A, patients in quintile 1 had a low risk of HF/death, quintiles 2 to 4 demonstrated an intermediate risk, and quintile 5 showed the highest risk of HF/death with a 5-year cumulative probability of

<table>
<thead>
<tr>
<th>End Point*</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF or death (50 events/185 patients)</td>
<td>PR (\geq 230) vs PR &lt;230 ms (17 vs 33 events)</td>
<td>3.28</td>
<td>1.72–6.26</td>
</tr>
<tr>
<td>HF only (45 events/185 patients)</td>
<td>PR (\geq 230) vs PR &lt;230 ms (16 vs 29 events)</td>
<td>3.56</td>
<td>1.82–6.98</td>
</tr>
<tr>
<td>All-cause mortality (20 events/185 patients)</td>
<td>PR (\geq 230) vs PR &lt;230 ms (8 vs 12 events)</td>
<td>3.56</td>
<td>1.34–9.51</td>
</tr>
</tbody>
</table>

HF indicates heart failure; ICD, implantable cardioverter defibrillator; and LBBB, left bundle branch block.

*Data were available in 185 of 207 patients with non-LBBB and an implanted ICD. Model is adjusted for age dichotomized at 65 years, diabetes mellitus, left ventricular end-systolic volume index at baseline, HF hospitalization before enrollment, diastolic blood pressure, atrial arrhythmia before enrollment, glomerular filtration rate \(\geq 60\), and smoking at baseline.

Figure 2. Kaplan–Meier estimates of the cumulative probability of (A) heart failure (HF)/death episodes in patients with PR \(\geq 230\) ms, (B) all-cause mortality in patients with PR \(\geq 230\) ms, (C) HF or death in patients with PR <230 ms, and (D) all-cause mortality in patients with PR <230 ms. CRT-D indicates cardiac resynchronization therapy with defibrillator; and ICD, implantable cardioverter defibrillator.
68%, suggestive of a threshold effect. When evaluating the effect of CRT-D versus ICD by baseline PR interval quintiles, there was a transition from CRT-D worsening outcome toward clinical benefit across increasing PR interval quintiles (Figure 3B).

Sensitivity Analyses
We performed separate analysis in patients with RBBB and IVCD and had consistent results (data not shown). We also evaluated the effect of the programmed AV delay on our findings. Patients with a long PR interval at baseline had significantly longer AV delays programmed compared with those with a normal PR interval (median of 160 versus 130 ms; P = 0.02). However, our results were confirmed after adjusting for AV delay in the multivariable model using either a continuous or a dichotomized value of AV delay.

Discussion
Our study demonstrates that non-LBBB patients with a long PR interval derive a significant clinical benefit from the implantation of CRT-D versus ICD-only. However, non-LBBB patients implanted with CRT-D with a normal PR interval have an increased risk of all-cause mortality compared with ICD-only therapy, suggesting a significant bidirectional interaction between baseline PR interval and clinical benefit from CRT-D in the non-LBBB population. Furthermore, we confirmed that PR interval is a powerful prognostic marker of cardiac events in patients with non-LBBB, mild HF, and a wide QRS.

Our data confirm previous results on the adverse prognostic significance of a prolonged PR interval in advanced HF and a wide QRS derived from the control group of the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure Trial (COMPANION) study.5

In mild HF patients with non-LBBB, severely depressed LV ejection fraction, and a marked PR prolongation ≥230 ms, CRT-D therapy significantly reduced the risk of death or HF hospitalization. Importantly, both the risk of all-cause mortality and HF hospitalization were similarly and significantly diminished by CRT-D compared with ICD-only patients in the prolonged PR group. In contrast, in non-LBBB patients with a normal or only slightly prolonged PR, CRT-D was associated with a trend toward a deleterious effect of the combined clinical end point, which was predominantly driven by a >2-fold increase in all-cause mortality. These findings suggest that patients with non-LBBB may be exposed to harm through CRT-D if they have a normal PR interval.

The strong bidirectional predictive value of the baseline PR interval for benefit versus adverse effects from CRT-D versus ICD therapy in non-LBBB patients suggests that in the absence of LBBB, the correction of LV dyssynchrony might not be the principal mechanism of action by CRT. It is more likely that the restoration of the physiological AV sequence with improvement of LV diastolic filling and the abolishment of presystolic mitral regurgitation explain the benefit from CRT-D in patients with non-LBBB and a prolonged PR interval. However, CRT pacing might be superior to RV pacing in patients with non-LBBB because it would be less prone to induce LV dyssynchrony.

The underlying concept is well known. Small observational patient series on right ventricular dual chamber (DDD) pacing with a short AV delay in patients with severe HF and first degree AV-block have been reported in the early 1990s showing that patients improve HF symptoms.14 A follow-up study postulated the sustained symptomatic benefit from right ventricular DDD pacing but reported a >75% mortality in 3 years.15 The evidence for the deleterious effects of right ventricular DDD pacing in HF patients with a severely depressed LV ejection fraction came from the Dual Chamber and VVI Implantable Defibrillator Trial (DAVID) reporting significantly more HF hospitalization or death in the DDD group versus VVI (ventricular) pacing at a lower rate of 40 bpm.16

Interestingly, a substudy from the DAVID trial showed that the outcome with DDD pacing versus VVI was similarly unfavorable in patients with a long PR (>200 ms).17 Hence, introducing dyssynchrony by right ventricular pacing in patients with HF outweighed the benefit from improved AV timing.

As shown later by the DANPACE (Danish multicenter randomised trial on single lead atrial versus dual chamber pacing in sick sinus syndrome) trial, the balance between
pacing-induced dyssynchrony and treatment of long PR may be different in patients with predominantly normal ejection fraction and a pacemaker indication. In this trial, patients with symptomatic sick sinus syndrome were randomized to AAI (atrial) versus DDD pacing, with the DDD arm specifically being oriented for treatment of first-degree AV block if the PR interval was >220 ms. With that programming, DDD patients had less atrial fibrillation and no disadvantage concerning HF or survival.

Our results suggest that non-LBBB mild HF patients with a near-normal (<230 ms) PR do not benefit from CRT. This may be because of several underlying mechanisms. The first aspect is that despite diminishing ventricular dyssynchrony in patients with LBBB, biventricular pacing may further increase ventricular dyssynchrony in those without LBBB. This has been reported to occur in HF patients with a narrow QRS and may also apply to non-LBBB patients with a wide QRS. Patients with a normal PR and wide QRS, but without LBBB, may further impair LV dyssynchrony and LV performance and not benefit from biventricular pacing. Another explanation might be that inappropriately short AV delays could have impaired the LV filling phase, thereby worsening LV performance.

Our study, however, has certain limitations. This analysis is a secondary analysis of MADIT-CRT that was not designed to evaluate differences within the non-LBBB group. The number of patients with a long PR interval within the non-LBBB cohort is relatively small; however, the results are strikingly different. Reproducibility of measurement of PR interval has not been assessed; however, it was performed in the Electrocardiography Core Laboratory. We do not have data on whether an AV optimization was performed in this patient group; however, our results have been consistent when adjusting for the programmed AV interval in the study. P values were not adjusted for multiple testing and should be considered nominal.

Our study suggests a new potential field for CRT in patients with non-LBBB and provides important clinical implications.

**Conclusions**

In summary, we demonstrated that mild HF patients with non-LBBB and a prolonged PR interval have a higher risk of cardiac events without CRT-D but derive significant clinical benefit from the implantation of a CRT-D system compared with ICD-only. Non-LBBB patients with a normal PR interval have an increased mortality risk from CRT-D compared with ICD therapy. Our data support the use of CRT-D in mild HF patients with non-LBBB and a prolonged (≥230 ms) PR interval. Additional analyses and randomized trials are warranted in this field.

**Acknowledgments**

We thank the patients, physicians, and centers for their dedication to the Multicenter Automatic Defibrillator Implantation Trial–Cardiac
Disclosures
The Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) study was supported by a research grant from Boston Scientific, St. Paul, Minnesota, to the University of Rochester School of Medicine and Dentistry. M. Stockburger was supported by research grants by Biotronik, Boston Scientific, Medtronic, and Sorin Group. J. Daubert received honoraria, research grant, and fellowship support from Boston Scientific. F. Holmquist was supported by travel grants from Sweden-America Foundation, Swedish Heart-Lung Foundation, Swedish Heart Association, and the Fulbright Commission. H. Klein received research grant and speaker honoraria from Boston Scientific. B. Olshansky is consultant speaker for Boston Scientific, Medtronic, consultant for BioControl, Daichi Sankyo, Boehringer Ingelheim, DSMB member for Amarin, Boston Scientific, and Sanofi Aventis. V. Kutyifa, C. Schuger, B. Merkely, W. Zareba, and A.J. Moss received research grant from Boston Scientific. S. McNitt reports no conflicts.

References

CLINICAL PERSPECTIVE
A substudy analysis from the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) study that showed that benefit from cardiac resynchronization therapy (CRT) in mild heart failure was confined to patients with left bundle branch block (LBBB). In this substudy, we report that the subgroup of non-LBBB patients who had a prolonged PR interval did benefit from CRT with defibrillator, with a 73% reduction in the risk of heart failure or death and 81% reduction in the risk of all-cause mortality compared with ICD-only therapy. In non-LBBB patients with normal PR, CRT with defibrillator therapy was associated with a trend toward an increased risk of heart failure or death and a >2-fold higher mortality compared with ICD therapy, suggesting a bidirectional significant interaction. Thus, our data support the use of CRT with defibrillator in non-LBBB patients with PR interval prolongation who fit MADIT-CRT entry criteria, including left ventricular ejection fraction <30%, QRS duration ≥130 ms, and mild heart failure (New York Heart Association I or II for ischemic disease, II for nonischemic cardiomyopathy). In non-LBBB patients with a normal PR interval, implantation of a CRT with defibrillator may be deleterious.
PR Interval Identifies Clinical Response in Patients With Non–Left Bundle Branch Block: A Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy Substudy

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_Circ Arrhythm Electrophysiol._ 2014;7:645-651; originally published online June 24, 2014;
doi: 10.1161/CIRCEP.113.001299

_Circulation: Arrhythmia and Electrophysiology_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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