Risk factors for ventricular tachyarrhythmic events in patients without left bundle branch block who receive cardiac resynchronization therapy

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Abstract

Introduction: Cardiac resynchronization therapy (CRT) may be pro-arrhythmic in patients with non-left bundle branch block (non-LBBB). We hypothesized that combined assessment of risk factors (RF) for ventricular tachyarrhythmias (VTAs) can be used to stratify non-LBBB patients for CRT implantation.

Methods: The study comprised 412 non-LBBB patients from MADIT-CRT randomized to CRT-D (n = 215) versus ICD only (n = 197). Best-subset regression analysis was performed to identify RF associated with increased VTA risk in CRT-D patients without LBBB. The primary end point was first occurrence of sustained VTA during follow-up. Secondary end points included VTA/death and appropriate shock.

Results: Four RFs were associated with increased VTA risk: blood urea nitrogen >25mg/dl, ejection fraction <20%, prior nonsustained VT, and female gender. Among CRT-D patients, 114 (53%) had no RF, while 101 (47%) had ≥1 RF. The 4-year cumulative probability of VTA was higher among those with ≥1 RF compared with those without RF (40% vs. 14%, p < .001). Multivariate analysis showed that in patients without RF, treatment with CRT-D was associated with a 61% reduction in VTA compared with ICD-only therapy (p = .002), whereas among patients with ≥1 RF, treatment with CRT-D was associated with a corresponding 73% (p = .025) risk increase. Consistent results were observed when the secondary end points of VTA/death and appropriate ICD shocks were assessed.

Conclusion: Combined assessment of factors associated with increased risk for VTA can be used for improved selection of non-LBBB patients for CRT-D.

Keywords
cardiac resynchronization therapy, non-left bundle branch block, pro-arrhythmic effect, risk factors, ventricular tachycardia

Clinical trial registration: http://clinicaltrials.gov/ct2/show/NCT00180271

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1 | INTRODUCTION

Cardiac resynchronization therapy (CRT) was shown to improve symptoms and decrease mortality in patients with heart failure (HF) with a wide QRS (Anand et al., 2009; Bradley et al., 2003; Cleland et al., 2012). However, data on the benefit of the device by QRS morphology are conflicting. Current ESC Guidelines provide a Class II recommendation for CRT-D implantation in patients without left bundle branch block (LBBB) (Brignole et al., 2013), yet several randomized studies have reported on the relative absence of clinical benefit of CRT in non-LBBB patients compared to those with LBBB. (Bertoldi et al., 2011) Therefore, studies on improved risk stratification for CRT-D in patients without LBBB are needed.

Recent studies have attempted to identify subgroups of non-LBBB patients who may respond clinically to CRT, such as those with prolonged PR intervals (≥230 ms) (Kutyifa et al., 2014) or those with (RBBB) with concomitant left-sided delay and those with significant burden of right ventricular pacing, with conflicting results (Pastore et al., 2018). Our data from MADIT-CRT suggest a possible harm, with increased risk for ventricular tachyarrhythmias (VTAs) among non-LBBB patients implanted with a CRT-D device compared with implantable cardioverter-defibrillator (ICD)-only therapy. (Goldenberg et al., 2014; Roque et al., 2014) The exact pathophysiology behind this observation remains unclear; however, these findings indicate a possible pro-arrhythmic effect of CRT in this population that may lead to subsequent adverse outcomes (Deif et al., 2018; Fish et al., 2004, 2005; Medina-Ravell et al., 2003).

Accordingly, the primary aim of the present study was to identify risk factors (RF) for VTA in patients without LBBB who were enrolled in MADIT-CRT. We hypothesized that combined RF assessment can be used to identify those in whom CRT implantation would beneficial versus pro-arrhythmic.

2 | METHODS

2.1 | Study population

The present study cohort comprised 412 patients from MADIT-CRT with non-LBBB, and complete information on baseline clinical, electrocardiographic, and laboratory variables was available. The rationale and design of the MADIT-CRT trial was previously published. (Moss et al., 2005) Briefly, MADIT-CRT was designed to determine whether CRT with a defibrillator (CRT-D) would reduce the risk of death or HF events in patients with mild HF symptoms, a reduced ejection fraction, and wide QRS complex compared with ICD therapy. Patients were randomly assigned in a 3:2 ratio to receive either CRT-D or ICD. From December 22, 2004, through April 23, 2008, a total of 1,820 patients were enrolled at 110 hospital centers. The protocol was approved by the institutional review board at each of the participating centers. Patients of either sex who were at least 21 years of age were enrolled in the study if they had ischemic cardiomyopathy (NYHA class I or II) or nonischemic cardiomyopathy (NYHA class II only), sinus rhythm, an ejection fraction of ≤0.30, and prolonged intraventricular conduction with a QRS duration of ≥130 milliseconds. All eligible subjects met guideline indications for ICD therapy. Of the 412 patients without LBBB who were included in the present study, 215 were randomized to CRT-D therapy and 197 were randomized to ICD-only therapy.

2.2 | End points and rhythm adjudication

The primary end point of this study was the first occurrence of VTA. Secondary end points were as follows: composite of VTA/death (whichever comes first) and appropriate defibrillator shock therapy. All device therapies delivered were blindly adjudicated by 2 experienced electrophysiologists. VTA was defined as any ICD-recorded, treated, or monitored sustained ventricular tachycardia (VT) faster or equal to 180 bpm or ventricular fibrillation (VF).

2.3 | Statistical analysis

Continuous variables are expressed as mean ± SD. Categorical data are summarized as frequencies and percentages. Baseline clinical characteristics were compared between patients with ICD, low-risk CRT-D, and high-risk CRT-D, using Wilcoxon ranked sum test for continuous variables and chi-square test for dichotomous variables, as appropriate.

2.3.1 | Step 1—covariate selection

We included 29 potential clinical, electrocardiographic, and laboratory binary risk factors for VTA (listed in Table S1 in the Online Appendix). Numeric variables were made binary by the use of cut points with the goal of finding a simple, easily implemented predictors to be derived from them. Thresholds for categorization of numeric variables were based on the mean or clinical relevance. Univariate relationships between candidate covariates and a further event were assessed by t tests (2 for binary responses). The covariates with values of p < .20 were further evaluated by carrying out a best-subset regression analysis, examining the models created from all possible combinations of predictor variables, and using a penalty of 3.84 on the likelihood ratio 2 value for any additional factor included (corresponds to a P of 5% for a 1-df 2 test).

2.3.2 | Step 2—Creating the groups

For the main analysis, CRT-D patients were grouped into two groups based on the presence or absence of RF. In a secondary analysis, we further grouped CRT-D patients into 3 groups: (a) no RF, (b) one RF, and (c) two or more RF. Since the identified CRT-D RF were not associated with outcomes in the ICD group (online supplemental Figure
FIGURE 1  (a) Cumulative probability of the primary end point (VTA) among non-LBBB patients with CRT-D stratified by the presence or absence of risk factors. (b) Cumulative probability of VTA/death stratified by the presence or absence of risk factors. (c) Cumulative probability of defibrillator appropriate shock therapy stratified by the presence or absence of risk factors.
S1), ICD patients were not further grouped and were included as a control group.

2.3.3  Step 3—Outcomes by score analysis

Kaplan–Meier estimates for any VTA, VTA/death, and appropriate shock in patients with ICD and CRT-D, stratified by their risk, were determined and statistically evaluated with the log-rank test. Multivariate Cox proportional hazards regression analyses were carried out in the subgroups for the assessment of the primary and secondary end points. The following covariates were included in the Cox regression models: age, gender, QRS width, New York Heart Association class NYHA, creatinine, left ventricular ejection fraction, diabetes, and ischemic origin.

All statistical tests were two-sided; a p-value of <.05 was considered statistically significant. Analyses were carried out with SAS software (version 9.4, SAS Institute, Cary, North Carolina).

3  |  RESULTS

3.1  |  Predictors of increased risk for ventricular arrhythmia and risk score

A best-subset regression analysis in the CRT-D arm of the trial identified 4 factors (from the 29 candidate covariates listed in Table S1 in the online-only data supplement) as being associated with increased risk for VTA (Table S2). These factors were blood urea nitrogen (BUN) >25 mg/dl, left ventricular ejection fraction <20%, prior nonsustained ventricular tachycardia (NSVT), and female gender.

The baseline clinical characteristics of study patients by the presence of VTA RF in CRT-D patients and the total ICD group are presented in Table S3. Mean age of the study patients was 65 ± 10 years, and 10% were female. Patients with ≥1 RF for VTA comprised 47% of the CRT-D population and had similar baseline characteristics as those without RF, with the exception of a higher baseline creatinine, and a higher frequency of diuretic use. Among the group of CRT-D patients with ≥1 RF, 82% had only 1 RF, while 17 patients (17%) had two RF, and only two patients (1%) had three RF.

3.2  |  Association of VTA RFs with outcomes in CRT-D patients without LBBB

Figure 1a shows that among non-LBBB patients with CRT-D, the 4-year cumulative probability of VTA was significantly higher among those with ≥1 RF when compared to those without RF (40% vs. 14%, p < .001, respectively). Similarly, patients with ≥1 RF experienced a significant higher rate of the secondary outcome measures of VTA/death (51% vs. 22%, respectively, log-rank p < .001 for the overall difference during follow-up [Figure 1b]) and appropriate ICD shock (28% vs. 7%, respectively; p = .002 [Figure 1c]).

Results also showed a dose response regarding the number of RF. At 3 years, the rate of VTA was highest among those with ≥2 RFs, attenuated in the one RF group, and was the lowest in the no RF group (47%, 37%, and 17%, respectively; p < .001; online supplementary Figure S2). Consistent results were seen for the secondary end points of VTA/death and appropriate ICD shock. Of note, patients with 2 RFs (n = 17) were combined with patients with 3 RFs (n = 2) due to the small size of the 3 RF group; no patients had 4 RFs.

The results of the CRT-D-only multivariate Cox regression models are presented in Table 1. Among non-LBBB patients with CRT-D, the presence of one or more RF was associated with >3.5-fold (p < .001) increased risk for VTA compared with no RF. Furthermore, patients who had 2 or more RF experienced a >9-fold (p < .001) increased risk for VTA compared with those with no RF. Similar results were shown for the secondary end points of VTA/death and appropriate ICD shock (Table 1).

| End point | Hazard ratio | 95% CI | p-value |
|-----------|--------------|--------|---------|
| Primary End Point: VTA | | | |
| ≥One Risk Factors versus No Risk Factors | 3.61 | 1.79–7.33 | <.001 |
| ≥Two Risk Factors versus No Risk Factors | 9.87 | 3.03–32.1 | <.001 |
| Secondary End Point: Death/ or VTA | | | |
| ≥One Risk Factors versus No Risk Factors | 3.34 | 1.79–6.23 | <.001 |
| ≥Two Risk Factors versus No Risk Factors | 7.31 | 2.47–21.6 | <.001 |
| Secondary End Point: Appropriate Shock Therapy | | | |
| ≥One Risk Factors versus No Risk Factors | 5.21 | 2.09–12.9 | <.001 |
| ≥Two Risk Factors versus No Risk Factors | 15.5 | 3.20–74.8 | <.001 |

Abbreviations: CRT-D, cardiac resynchronization therapy with defibrillator; HF, heart failure; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; VTA, ventricular tachyarrhythmia.

Model were adjusted for age, gender, QRS length, creatinine, left ventricular ejection fraction, New York Heart Association score, diabetes, and ischemic origin.

Supplementary Table 1.
3.3 | Benefit of CRT-D versus ICD-only therapy by VTA risk score

Among all non-LBBB patients enrolled in MADIT-CRT (i.e., with ICD or CRT-D), the 4-year cumulative probability of VTA was highest among CRT-D patients with RF (40%), intermediate in the ICD group (33%), and lowest among CRT-D without RF ([14%], log-rank \( p < .001 \) for the overall difference during follow-up [Figure 2: left panel]). Similarly, the 4-year cumulative probability of the composite of death or VTA was 51% in CRT-D patients with RF, 42% in the ICD-only group, and 22% in the CRT-D group without RF (log-rank \( p < .001 \) for the overall difference during follow-up [Figure 2: middle panel]); and the respective rates of appropriate defibrillator shock therapy were 28%, 19%, and 7%, respectively (log-rank \( p = .008 \) for the overall difference during follow-up [Figure 2: right panel]).

Multivariate analysis showed that among non-LBBB patients with no RF, treatment with CRT-D therapy was associated with a statistically significant 61% \( (p = .002) \) reduction in the risk of the primary VTA end point compared with ICD-only therapy. Similar results were shown for the secondary end points, wherein treatment with CRT was associated with a significant 50% \( (p = .011) \) reduction in VTA/death and a significant 52% \( (p = .079) \) reduction in the risk of appropriate ICD shock therapy (Table 2). In contrast, among non-LBBB patients who had one or more RF, treatment with CRT-D was associated with a statistically significant 73% \( (p = .025) \) increase in the risk of VTA, a 72% \( (p = .014) \) increase in the composite end point of VTA/death, and a 91% \( (p = .043) \) increase in the risk of appropriate defibrillator shock therapy (Table 2).

4 | DISCUSSION

In the present study, we provide several important insights on predictors for VTA outcomes in CRT-D patients with non-LBBB, in whom data on the potential benefit of the device are limited and conflicting. First, we identified 4 simple baseline clinical factors (BUN > 25mg/dl, EF < 20%, prior NSVT, and female gender) that were associated with increased risk for VTA in CRT-D patients with non-LBBB. Second, we have shown that among patients without any of the identified RF, treatment with CRT-D was associated with a significant reduction in the risk of arrhythmic events compared with ICD-only therapy, including any VTA, VT/death, and appropriate defibrillator shocks. In contrast, among patients with at least one RF, treatment with CRT-D was associated with a possible pro-arrhythmic
effect, wherein the risk of any VTA, VTA/death and appropriate de-
fibrillator shocks was significantly higher among patients implanted
with a CRT-D device compared with those treated only with an ICD.
These findings suggest that combined assessment of simple base-
line clinical parameters can be used to distinguish CRT-D candidates
without LBBB who may benefit from biventricular pacing compared
with those in whom CRT-D may be possibly be associated with a
harmful pro-arrhythmic effect.

In a meta-analysis of the five landmark randomized controlled
trials evaluating CRT in the HF population, with a total of 1766
patients with non-LBBB QRS morphology at baseline, the use of
CRT was not associated with a significant reduction in mortal-
ity or HF hospitalizations. (Cunnington et al., 2015) Moreover,
among non-LBBB patients the use of CRT-D was suggested to
be harmful and possibly associated with increased all-cause
mortality when compared with ICD alone. (Bilchick et al., 2010;
Goldenberg et al., 2014) The mechanism related to the observed
trend in mortality increase associated with CRT-D in non-LBBB
patients remains unclear. We have previously shown that in
MADIT-CRT non-LBBB patients who were randomized to CRT-D
therapy experienced a significant 3.6-fold ($p = .009$) increased
risk for recurrent VTAs compared with ICD-only patients. (Ouellet
et al., 2012) These findings may be due to a pro-arrhythmic effect
of CRT among patients without LBBB leading to increased risk
associated with the device in this population. These data are con-
sistent with previous studies, including a large comprehensive
meta-analysis, which reported on the pro-arrhythmic effect of
CRT among nonresponders to the device. (Deif et al., 2018; Fish
et al., 2004, 2005; Medina-Ravell et al., 2003) A potential mech-
anism for the pro-arrhythmic role of CRT-D in non-LBBB patients
is the reversal of left ventricular activation and increased trans-
mural dispersion of repolarization with epicardial pacing, thus
allowing for the development of early after depolarizations and
re-entrant circuits. (Medina-Ravell et al., 2003) Despite the
above-mentioned observations, current ESC Guidelines provide
a Class II recommendation (with a or b level based on QRS dura-
tion) for CRT in non-LBBB patients. (Brignole et al., 2013) Based
on this recommendation, approximately one quarter of CRT-D
implants from 2012 to 2015 through the National Cardiovascular
Data Registry for Implantable Cardioverter-Defibrillators were in
patients who had a non-LBBB morphology at baseline. (Sandhu
et al., 2019).

4.1 | Predictors for ventricular arrhythmia

In the present study, we identified 4 factors that were associated
with increased risk of VTA, including BUN $> 25$mg/dl, EF $< 20$%,
prior NSVT, and female gender. Reduced EF and prior NSVT re-

don't enter the final prediction model.

Several previous publications have suggested that women may
respond better to CRT with subsequent lower mortality than men.
(Cheng et al., 2014; Loring et al., 2013) Our study suggests that
among patients without LBBB, the effect of sex may be different
and that non-LBBB women may experience increased VTA risk with
CRT-D. These data are consistent with our prior findings from the
long-term follow-up of MADIT-CRT, in which we have shown that
the pronounced benefit of CRT for the end point of all-cause mor-
tality among women was restricted to those with LBBB, whereas
CRT-D was associated with a trend to a mortality risk increase
among women without LBBB.

One wonders if the absence of these findings identifies an indi-

cate a more advanced and complex condition whereby QRS
prolongation is a secondary event.

4.2 | The effect of CRT in non-LBBB

In contemporary practice, the use of CRT in non-LBBB patients re-
mains controversial, mainly due to high rates of nonresponse among
such patients. In previous studies, PR prolongation was identi-
fied as a strong predictor for CRT response in non-LBBB patients.
Interestingly, in our study PR prolongation did not predict the oc-
currence of VTA, or VTA and death. However, the mechanism in
which CRT reduces heart failure hospitalization is entirely distinc-
tive than the mechanism in which CRT may be pro-arrhythmic. In
our study, with the utilization of simple RF, we were able to identify
a large group of patients without RF, in whom CRT is potentially ben-
eficial and may be associated with an anti-arrhythmogenic effect.
This group of non-LBBB patients may therefore derive benefit from
treatment with cardiac resynchronization therapy. In contrast, in
non-LBBB patients with $\geq 1$ RF, implantation of CRT-D was associ-
ated with increased risk of VTA, VTA/death, and appropriate defi-
brillator shocks, suggesting a possible pro-arrhythmic effect. Thus,
this group of non-LBBB patients may experience improved out-
comes with ICD therapy alone rather than combined with cardiac
resynchronization therapy.

4.3 | Limitations

It should be noted that our findings, based on a subanalysis of the
MADIT-CRT trial, should be considered as hypothesis generating
since other unmeasured variables in the MADIT-CRT data set may
have further contributed to the observed outcomes. Accordingly,
the present findings need to be further validated in prospective
studies that will be appropriately design to identify LBBB patients
who may derive benefit versus harm from CRT implantation. At
present, we believe that our data can be used to enhance decision support in this high-risk and understudied population. Furthermore, the current analysis utilizes patient data from MADIT-CRT cohort, with specific enrollment selection criteria. Thus, the findings of the present study are applicable only to patients with mild heart failure symptoms enrolled in the trial.

5 CONCLUSIONS AND CLINICAL IMPLICATIONS

Our study suggests that baseline factors that are associated with increased risk for VTA can be used to identify non-LBBB patients in whom CRT-D may associate with beneficial versus pro-arrhythmic effects. These findings, if appropriately validated in similar populations of CRT-D recipients and larger studies, may be used for improved selection of patients with non-LBBB for cardiac resynchronization therapy with a defibrillator versus ICD-only therapy.

CONFLICT OF INTEREST

WZ, VK, and IG have received research grants from Boston Scientific. All other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data belongs to the University of Rochester, NY and Boston Scientific. Data might be available based on upon request.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.