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Postimplantation ventricular ectopic burden and clinical outcomes in cardiac resynchronization therapy-defibrillator patients: a MADIT-CRT substudy

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Background: Frequent ventricular ectopy on preimplantation Holter has been associated with attenuated benefit from cardiac resynchronization therapy (CRT). However, it is unclear whether ectopic burden measured post-CRT implantation can be utilized to evaluate long-term prognosis. We aimed to describe the association between post-CRT implantation ectopic burden and subsequent risk of clinical outcomes.

Methods: At the 12-month follow-up visit, 24-hour Holter recordings were performed in 698 CRT-D patients from the MADIT-CRT study. The mean number of ventricular premature complexes (VPCs/hour) was calculated. High ectopic burden was defined as >10 VPCs/hour and low burden as ≤10 VPCs/hour. Multivariate Cox proportional hazards models were utilized to assess the association between 12-month ectopic burden and the risk of the end points of heart failure (HF) or death and ventricular tachyarrhythmias (VT/VF).

Results: At 12 months, 282 (40%) patients presented with low ectopic burden and 416 (60%) patients presented with high ectopic burden. The 3-year risk of HF/death and VT/VF was lower in patients with a low burden (7% and 8%) and significantly higher (25% and 24%) in patients with high burden. In multivariate analyses, patients with a high ectopic burden had approximately threefold increased risk of both HF/death (HR=2.76 [1.62–4.70], $p < .001$) and VT/VF (HR=2.79 [1.69–4.58], $p < .001$).

Conclusion: In CRT-D patients with mild heart failure, high ectopic burden at 12-month follow-up was associated with a high 3-year risk of HF/death and VT/VF and threefold increased risk as compared to patients with low burden. Ectopic burden at 12 months may be a valuable approach for evaluating long-term prognosis.

KEYWORDS
appropriate therapy, cardiac resynchronization therapy, death, heart failure, premature beats, ventricular ectopy, ventricular tachycardia

1 | INTRODUCTION

The beneficial effects of cardiac resynchronization therapy with defibrillator (CRT-D) in heart failure (HF) patients with depressed left ventricular function and electromechanical delay have been widely established (Brignole et al., 2013). However, the efficacy of CRT-D relies on the ability of the device to maintain a high level of biventricular (BIV) pacing, preferably above 97% (Hayes et al., 2011; Koplan et al., 2009; Ruwald et al., 2015). Effective BIV-pacing capture can be affected by several potentially modifiable factors, including the duration of the programmed atrioventricular delay (AV-delay), atrial and ventricular arrhythmias, including premature ectopic beats (Cheng, Landman, & Stadler, 2012; Ruwald, Mittal et al., 2014). Recently, it was shown that ectopic burden above 0.1% on 24-hour Holter, measured before CRT-D implantation, was associated with reduced overall BIV-pacing percentage and significantly worse outcome, indicating that preimplantation Holter monitoring could be an effective tool for patients selection (Ruwald, Mittal et al., 2014).

Although methods for patient selection are priority, a number of patients do not derive the expected benefit from CRT-D implantation (Abraham et al., 2002; Ge et al., 2014; Padeletti, Paoletti Perini, & Gronda, 2012). These patients may derive advantage from post-implantation pharmacologic optimization, radiofrequency ablation, and/or modified device programming to achieve greater BIV-capture and thus a better utilization of the CRT-D device (Lakkireddy et al., 2012). Therefore, tools for evaluating CRT-D efficacy post-implantation are needed. Postimplantation 24-hour Holter monitoring might prove to be an inexpensive, easy-to-use tool for identifying patients who might benefit from the above-mentioned initiatives and for evaluating the projected long-term prognosis. However, there is a paucity of studies investigating the clinical and predictive value of Holter monitoring in these patients.

We aimed to evaluate the association between 12-month ventricular ectopic burden and the risk of HF/death and malignant ventricular tachyarrhythmias in CRT-D patients with preexisting ischemic or nonischemic cardiomyopathy and mild HF symptoms from the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT). We hypothesized that low ectopic burden would be associated with better outcome and high ectopic burden would be associated with impaired clinical benefit. Furthermore, as a sensitivity analyses, we aimed to evaluate whether ectopy burden at 12 months or change in ectopic burden from implantation to 12 months is a better predictor of outcome.

2 | METHODS

2.1 | MADIT-CRT

The MADIT-CRT trial was a major randomized device trial conducted from December 22, 2004 through June 22, 2009 involving 1820 patients randomized in a 3:2 fashion for primary prevention CRT-D or ICD implantation. Inclusion criteria included depressed left ventricular (LV) function (LVEF<30%), prolonged QRS duration (>130 ms), ischemic (NYHA class I/II), or nonischemic (NYHA class II) cardiomyopathy and sinus rhythm at enrollment. Patients were excluded from randomization if they, within 3 months prior to enrollment, had undergone coronary bypass graft surgery, percutaneous intervention, or had experienced a myocardial infarction, or if they, within 1 month prior to enrollment, had experienced atrial fibrillation.

Patients were enrolled from 110 centers in the United States, Canada, and Europe, and extended follow-up with event adjudication was conducted until September 10, 2010.

The protocol from the MADIT-CRT trial has previously been published (Moss et al., 2005).

2.2 | Study population

The current study population was limited to the 698 CRT-D patients from the MADIT-CRT trial who had all undergone both preimplantation and 12-month 24-hour Holter monitoring (Figure 1). Follow-up was conducted in this analysis from 12 months after implantation, until end-of-follow-up (September 10, 2010) or the occurrence of the end point of interest.

2.3 | Holter recordings and definition of ectopic burden

Mortara H12 12-lead Holter recorders were used for all patients and data from the recordings were obtained by Mortara H-Scribe scanning system (Mortara Instruments, Milwaukee, WI, USA). A blinded Rochester electrocardiographic core laboratory analyzed and adjudicated all Holter recordings, as previously described (Ruwald et al., 2014). The precise monitoring period and the presence of ventricular premature complexes (VPC) were quantified, and the mean number of beats per hour was calculated. All annotations of beats were performed by an experienced Holter technician. All paper copies of Holter records were reviewed by arrhythmologist (WZ) and cases with doubts regarding beat annotation or identification of arrhythmias were reexamined.

Based on previous reports (Bogun et al., 2007; Cairns, Connolly, Roberts, & Gent, 1997; Ruwald et al., 2014), we predefined low and high ectopic burden as the following: *low ectopic burden* ≤10 VPCs/hour and *high ectopic burden* >10 VPCs/hour.

In sensitivity analyses, we investigated the prognostic significance of changes in ectopic burden on outcome. Based on preimplantation and 12-month postimplantation Holter recordings, we defined four groups of ectopic patterns:

1. *Unchanged low burden*, defined as patients who presented with both a low preimplantation and low 12-month ectopic burden
2. *Reduction in burden*, defined as patients who presented with a high preimplantation ectopic burden and a low 12-month ectopic burden
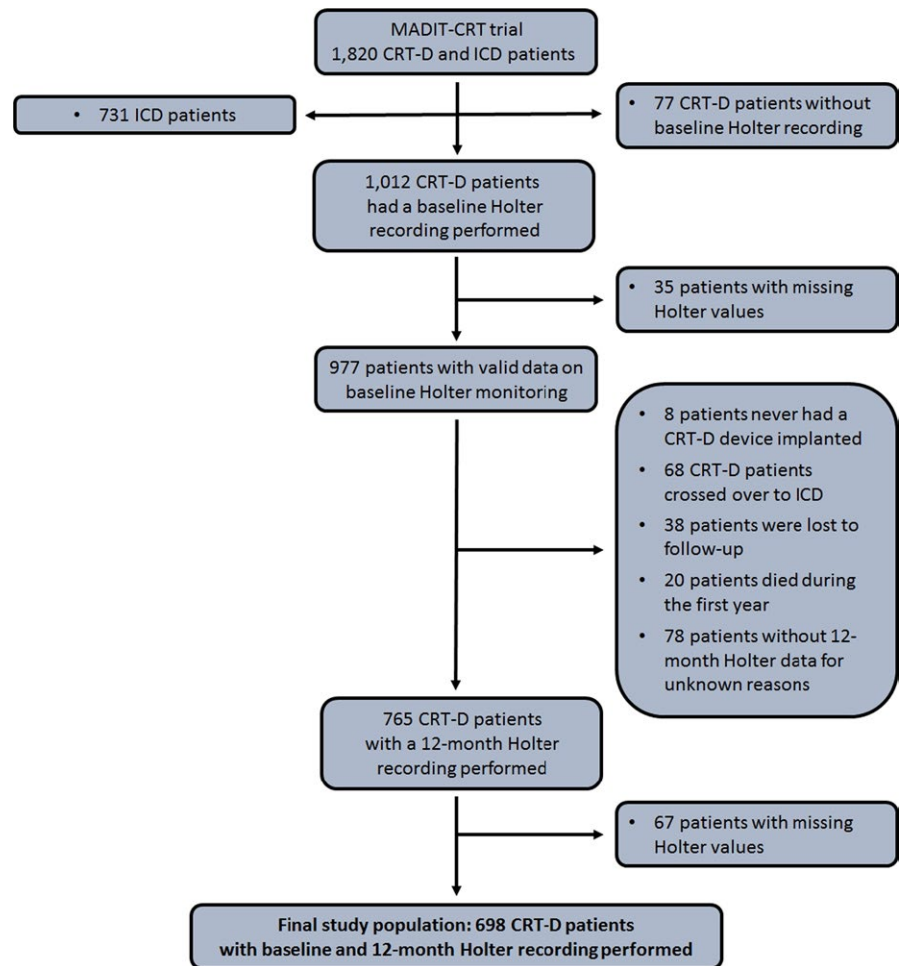
FIGURE 1 Study population flowchart. This flowchart depicts the selection of the 698 CRT-D patients from the MADIT-CRT trial that comprises the study population. Twenty-four-hour Holter recordings were performed. In the MADIT-CRT study, Holter monitoring was limited to patients randomized to CRT-D. CRT-D, cardiac resynchronization therapy with defibrillator. ICD, implantable cardioverter defibrillator

3. *Increase in burden*, defined as patients who presented with a low preimplantation ectopic burden and a high ectopic burden at 12-month follow-up

4. *Unchanged high burden*, defined as patients who presented with both a high preimplantation and high 12-month ectopic burden.

2.4 | Device implantation, programming, and interrogation

Boston Scientific CRT-D devices were implanted using conventional transvenous implant methods and programmed according to a pre-specified study protocol in DDD mode with a lower rate of 40 bpm and hysteresis off (Moss et al., 2005). It was recommended that AV-delay be programmed according to the latest optimization techniques.

Devices were programmed with a ventricular tachycardia (VT) zone set at 180 beats per minute (bpm) with a detection time of 2.5 seconds (s), and a ventricular fibrillation (VF) zone set at 210 bpm with a 1.0 s detection time. All supraventricular tachycardia (SVT) discriminators and anti-tachycardia pacing (ATP) were nominally programmed "on." Sensitivity was set at the discretion of the implanting physician.

Patients were scheduled for follow-up visits with device interrogation 1 month after implantation and thereafter every 3 months until the end of follow-up. Interrogation discs were sent to an independent central core laboratory, where an arrhythmia adjudication committee adjudicated all arrhythmias and therapies according to predefined definitions of appropriate and inappropriate ICD therapy (Moss et al., 2005). Appropriate ICD therapy was defined as anti-tachycardia pacing or ICD shock rendered for VT/VF.

2.5 | End points

The primary end point of the current study was defined as nonfatal events constituted the secondary end point.

An independent HF and mortality adjudication committee reviewed all HF and death events according to prespecified classifications (Moss et al., 2005). A nonfatal HF event was defined as symptoms consistent with congestive HF with one of the following; 1. intravenous decongestive therapy for more than 2 hr without hospital admission, or 2. hospital admission with oral or intravenous decongestive therapy (Moss et al., 2005). Ventricular tachyarrhythmia events were defined as appropriate ICD therapy for VT/VF, as adjudicated by the independent arrhythmia adjudication committee. The physicians were encouraged to program the device to detect

arrhythmias above or equal to 180 bpm; as a result, ventricular tachyarrhythmias <180 bpm were not considered in the current study.

2.6 | Statistics

Baseline characteristics were compared between patients with a low and high ectopic burden at 12 months, using chi-square test and Fisher's exact test for dichotomous variables and Kruskal–Wallis test for continuous variables.

Follow-up started at 12 months, as a landmark analysis, and the cumulative risk of the end points over time was illustrated by the Kaplan–Meier method. Comparisons between groups were calculated using the log-rank test.

Cox proportional hazard regression models were utilized to evaluate the relative risk of the end points between the groups, always starting follow-up at 12 months. Separate models were fitted for each of the end points, with adjustment variables found by best subset regression, setting the limit for entry into the model at $p < .05$. For the end point of HF/death, the following variables entered the model: diabetes, left bundle branch block (LBBB) QRS morphology, male gender, hospitalizations 1 year prior to enrollment, glomerular filtration rate<60 ml/min/m^2, and baseline LV end systolic volume indexed by body surface area (ml/m^2). For the end point of VT/VF, we adjusted for prior ventricular arrhythmias, QRS duration, male gender, and baseline LV end systolic volume indexed by body surface area (ml/m^2). Interactions were tested systematically and none were found. Logistic regression models were utilized to identify predictors of low ectopic burden at 12 months. Hazard ratios (HR) and odds ratios (OR) with their 95% confidence intervals (CI) and two-sided p values are reported. A two-tailed p value below .05 was considered statistically significant.

Analyses were performed using SAS statistical software 9.3 version (SAS Institute, Cary, NC, USA).

3 | RESULTS

3.1 | Ectopic burden at 12 months

Out of 698 CRT-D patients, 282 (40.4%) presented with low ectopic burden and 416 (59.6%) presented with high ectopic burden at 12 months. The mean follow-up duration was 2.23 ± 0.98 years.

There were significant differences in baseline characteristics between patients with a low (≤10 VPCs/hour) and high ectopic burden (>10 VPCs/hour) at 12 months (Table 1). Patients with a low ectopic burden presented with younger age, more often had nonischemic cardiomyopathy and a lower utilization of diuretics, and were more commonly female.

Furthermore, they presented with echocardiographic smaller ventricular and atrial volumes, more often had LBBB QRS morphology, had longer QRS duration, and experienced the greatest level of reverse remodeling from baseline to 1-year follow-up. No other differences in comorbidities and pharmacotherapy were evident between the groups.

3.2 | Association between postimplantation ectopic burden and the risk of VT/VF, HF/death, and death

Patients with a low ectopic burden at 12-month postimplantation had a very low risk of HF/death and VT/VF, with 3-year cumulative incidences of 7%and 8%, respectively, for the end points, significantly lower than for patients with high 12-month ectopic burden whose 3-year cumulative incidences were 25% and 24%, respectively (Figure 2). In multivariate Cox proportional hazard regression analyses, high ectopic burden was associated with a significant 2.8-fold increased risk of HF/death and VT/VF, as compared to patients with low ectopic burden (Table 2). No differential effect was found between patients with ischemic or nonischemic cardiomyopathy (p interaction=.071), or between LBBB and non-LBBB patients (p interaction=.287). To assess whether ectopic burden added additional prognostic value to echocardiographic measurements, we conducted a sensitivity analysis, adjusting for LVESV percentage change from baseline to 12-month follow-up, and found a significant association between the end points of HF/death and VT/VF and both LVESV percentage change (HF/death: HR = 1.03 [1.02–1.05], $p < .001$; VT/VF: HR = 1.02 [1.01–1.03], $p = .003$) and high ectopic burden (HR = 1.87 [1.02–3.45], $p = .044$; VT/VF: HR = 2.52 [1.37–4.63], $p < .003$).

Only 47 patients died during the follow-up, with significantly more in the high ectopic burden group (38, 9%), as compared with the low ectopic group (9, 3%). In multivariate analyses, high ectopic burden was associated with an increased risk of death although we did not have enough power to detect a significant difference between the groups (HR = 1.86 [0.87–3.95], $p = .109$).

3.3 | Change in ectopic burden

In sensitivity analysis, we investigated the changes in ectopic burden from preimplantation Holter to 12-month postimplantation Holter.

Out of 698 CRT-D patients with a preimplantation and 12-month Holter recording, 10 patients had no ectopy (0 VPCs) in preimplantation recording. Of the remaining 688 patients, 242 (35%) patients experienced a reduction ≥50% in the absolute number of VPCs/hour and 267 (40%) patients experienced an increase in ≥50% in the absolute number of VPCs/hour.

As described in the methods, we created four groups of change from preimplantation to 12 months burden. Within these groups, most patients had an unchanged high ectopic burden (>10 VPCs/hour) at 12 months (336 [48%] patients); 200 (29%) had an unchanged low ectopic burden (≤10 VPCs/hour) at 12 months, whereas 82 (12%) patients experienced a reduction (from >10 VPCs/hour to ≤10 VPCs/hour) and 80 (12%) patients experienced an increase in ectopic burden (from ≤10 VPCs/hour to >10 VPCs/hour).

Patient characteristics of all four groups of change are shown in the online appendix (Appendix S1).

Patients with an unchanged low ectopic burden and patients with a reduction in ectopic burden had a similar low risk of HF/death and VT/VF, with 3-year cumulative incidences of 7%–8% for both end

TABLE 1 Clinical characteristics in CRT-D patients with a low or a high burden of ventricluar ectopy at 12-month follow-up

Clinical Characteristics	Low burden N = 282	High burden N = 416
Female	103 (37)	75 (18)[*]
Age (years)	62.4 ± 10.9	65.5 ± 10.2[*]
Left bundle branch block	226 (80)	273 (66)[*]
QRS duration at baseline (ms)	162.0 ± 19.1	156.1 ± 19.0[*]
Heart rate (beats per minute)	67.2 ± 10.9	67.6 ± 10.5
Ectopic burden (VPCs/hour) (median with interquartile ranges)	2.2 [0.5–5.0]	68.0 [25.5–190.1]
BIV-pacing ≥97% (average at the end of follow-up)	229 (83)	218 (53)
Glomerular filtration rate (ml/min/1.73 m²)	71.3 ± 21.3	69.5 ± 20.6
Ischemic cardiomyopathy	119 (42)	250 (60)[*]
Prior myocardial infarction	90 (32)	190 (47)[*]
Diabetes	83 (29)	132 (32)
Hypertension	172 (61)	264 (64)
Past atrial arrhythmias	28 (10)	49 (12)
Past ventricular arrhythmias	15 (5)	31 (8)
Hospitalizations within the year prior to implantation	124 (44)	202 (49)
NYHA > II within 3 months prior to enrollment	31 (11)	42 (10)
Pharmacotherapy at baseline		
Antiarrhythmic drugs including amiodarone and sotalol	20 (7)	36 (9)
Amiodarone	19 (7)	26 (6)
ACE inhibitor or ARB	273 (97)	398 (96)
Beta-blocker	269 (95)	387 (93)
Digitalis	68 (24)	115 (28)
Diuretic	180 (64)	298 (72)[*]
Echocardiographic findings at baseline		
Left ventricular ejection fraction (%)	24.2 ± 5.2	23.9 ± 5.0
LVEDV indexed by BSA (ml/m²)	120.2 ± 24.9	125.5 ± 26.4[*]
LVESV Indexed by BSA (ml/m²)	85.1 ± 20.4	89.6 ± 21.3[*]
LAV indexed by BSA (ml/m²)	44.3 ± 9.4	47.1 ± 10.2[*]
Echocardiographic change from baseline to 1-year follow-up		

(Continues)

TABLE 1 (Continued)

Clinical Characteristics	Low burden N = 282	High burden N = 416
Left ventricular ejection fraction increase (% points)	12.9 ± 5.4	10.0 ± 5.0[*]
LVEDV % reduction (%)	24.6 ± 11.7	18.6 ± 10.8[*]
LVESV % reduction (%)	37.8 ± 14.9	29.4 ± 15.0[*]
LAV % reduction (%)	31.6 ± 12.0	26.0 ± 12.2[*]
CRT-D programming		
Programmed AV delay (msec)	114.1 ± 34.8	123.8 ± 38.6[*]
Cutoff rate of lowest VT zone (bpm)	177.3 ± 8.0	176.6 ± 8.3

CRT-D, cardiac resynchronization therapy with defibrillator; LVEDV, left ventricular end diastolic volume; BSA, body surface area; LVESV, left ventricular end systolic volume; LAV, left atrial volume; ACE, angiotensin-converting enzyme; ARB, angiotensin-II-receptor blocker.
Values are presented as mean with standard deviations or as crude numbers with percentages in parenthesis.
[*]p < .05.

points, whereas patients with an unchanged high ectopic burden, and patients who experienced an increase in ectopic burden had a significantly higher risk of HF/death and VT/VF, with 3-year cumulative incidences of 24%–25%. (Figure 3).

Multivariate Cox proportional hazard regression analyses confirmed that unchanged high ectopic burden and increased ectopic burden were both associated with a similar and significant twofold to threefold increased risk of HF/death and VT/VF, as compared to patients with an unchanged low ectopic burden (Table 2). No difference in the risk of HF/death or VT/VF was evident between patients who experienced a reduction in ectopic burden and patients with an unchanged low ectopic burden (p = .761 and p = .869). The same was true for patients with an unchanged high ectopic burden and patients who experienced an increase in ectopic burden (p = .397 and p = .406), indicating that the 12-month ectopic level was an equally good predictor of HF/death and VT/VF, as compared to groups of ectopic change. This was further tested statistically, where we found the two models (12-month ectopic burden vs. groups of ectopic change) to be almost identical when comparing the −2log likelihood values (HF/death: 1,214.250 vs. 1,214.250 and VT/VF: 1,315.782 vs. 1,316.538).

3.4 | Factors associated with low ectopic burden at 12 months

Using logistic regression, we identified independent predictors of low ectopic burden at 12 months. Female gender, LBBB QRS morphology, QRS duration>150 ms, blood urea nitrogen <25 mg/dl, younger age, and smaller left atrial volume all independently predicted low ectopic

(a) Probability of HF/death by 12-month ectopy level.
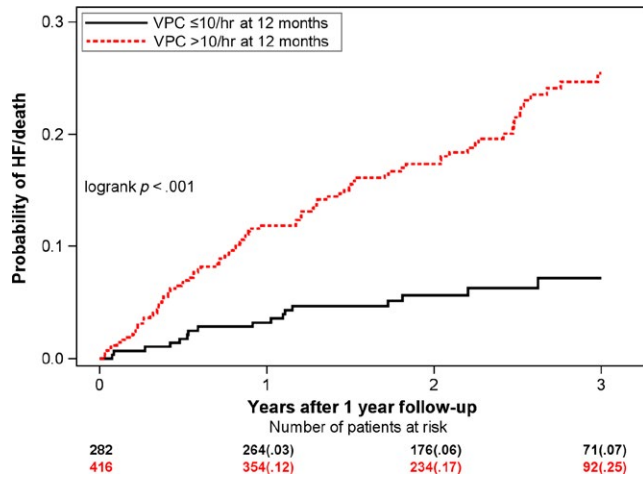
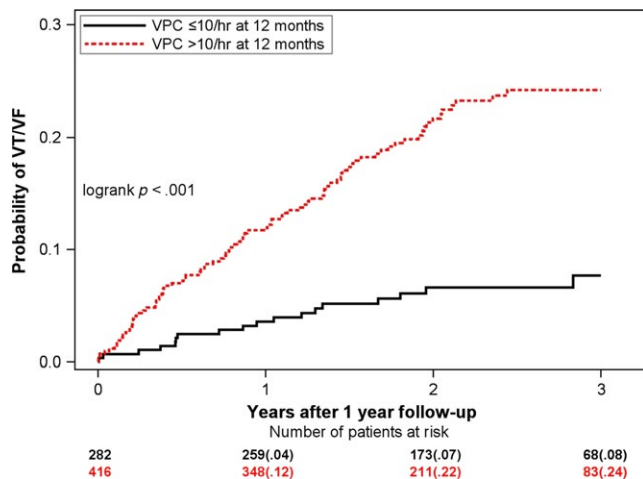**(b)** Probability of VT/VF by 12-month ectopy level.

FIGURE 2 Probability of outcome by 12-month ectopy level. Kaplan–Meier plots showing the probability of HF/death (a) and ventricular tachyarrhythmias (b) by low (black) or high (red) ectopic burden at 12-month follow-up. Ectopic level was evaluated by 24-hour Holter monitoring at the 12-month follow-up visit. Low ectopic burden is defined as ≤ 10 ventricular ectopic beats per hour. High ectopic burden is defined as >10 ventricular ectopic beats per hour

burden at 12 months (Table 3). Furthermore, low ectopy burden at 12 months was the single most significant factor associated with an overall high BIV-pacing percentage (>97%) (OR = 6.39 [3.85–10.56], $p < .001$).

4 | DISCUSSION

In the current study, we aimed to evaluate the association between postimplantation 12-month ectopic burden and clinical outcome in CRT patients. We found that patients with a high ectopic burden at 12 months after implantation had a significant and clinically relevant threefold increase in the risk of HF/death and VT/VF, when compared to patients with a low ectopic burden.

Furthermore, change in ectopic burden from preimplantation to 12 months after implantation was an equally good predictor of the end point, indicating that 12-month ectopic burden predicts subsequent outcome, irrespective of preimplantation ectopic burden.

The majority of patients implanted with a CRT-D device, who fulfill guideline criteria, derive a significant benefit from the device in terms of atrial and ventricular remodeling, improvement in NYHA symptoms, and overall better long-term prognosis (Ge et al., 2014; Goldenberg et al., 2014). However, patients remain, who do not experience the expected clinical benefit from cardiac resynchronization therapy. The efficacy of the device relies on effective BIV-capture, and thus electromechanical synchronization of the otherwise desynchronized ventricular contraction. Previous studies have shown that BIV-pacing >90% is needed to derive benefit from a CRT-D device although there is an additional significant clinical benefit in patients who achieve >97% BIV-pacing (Hayes et al., 2011; Koplan et al., 2009; Ruwald et al., 2015). There are a substantial number of potentially modifiable factors that may affect the BIV-capture, and thus the efficacy of the device. In recent studies from our group, we showed that even low ectopic levels measured prior to CRT-D implantation was associated with a significant increase in HF events and/or death, less reverse remodeling, as well as a higher likelihood of BIV-pacing <97% (Mittal et al., 2014; Ruwald et al., 2015; Ruwald, Mittal et al., 2014). Furthermore, Cheng et al. reported that frequent VPCs accounted for 17% of loss of BIV-capture in patients implanted with a CRT device (Cheng et al., 2012). In the current study, a 12-month low ectopic level was associated with 64% reduced risk of HF/death and VT/VF, as well as a six times higher likelihood of achieving BIV-pacing >97%. These findings complement the previous reported associations between higher levels of ectopy resulting in lower percentages of BIV-pacing (Cheng et al., 2012; Ruwald, Mittal et al., 2014). Furthermore, we found that female gender, left bundle branch block, longer QRS duration, lower age, smaller left atrial volumes, and superior renal status all independently predicted a 12-month low ectopic burden. These factors have all previously been reported to be associated with superior CRT-D response (van Bommel et al., 2009; Ge et al., 2014; Goldenberg et al., 2011; Ruwald et al., 2014; Van Bommel et al., 2011; Zareba et al., 2011).

This study emphasizes the importance of closely monitoring patients with regular follow-ups after CRT implantation to optimize the benefit of the device. The results suggest that 24-hour Holter monitoring may prove to be a valuable and cost-effective method for evaluating the current ectopic status and estimating long-term prognosis in mild heart failure patients implanted with a CRT-D device. It has been shown that radiofrequency ablation improves the efficacy of CRT-D in patients with frequent VPCs (Lakkireddy et al., 2012). Furthermore, some of these patients may benefit from antiarrhythmic drug suppression of ectopy or pharmacological optimization. Therefore, evaluating the burden of ectopy in CRT-D patients, both before and after implantation, could help guide clinicians to appropriate interventions that may optimize BIV-capture.

4.1 | Clinical implications

Estimating prognosis in patients' post–device implantation is important. Twenty-four hour Holter monitoring is an inexpensive and

TABLE 2 Risk of HF/death and ventricular tachyarrhythmias by ectopic burden

	HF/death				VT/VF			
	Events/patients (105/698)	Hazard ratio	95% CI	p Value	Events/patients (111/698)	Hazard ratio	95% CI	p Value
Ectopic burden at 12 months								
Ref: Low ectopic burden	17/282	1.00	1.00	NA	20/282	1.00	1.00	NA
High ectopic burden	88/416	2.76	1.62–4.70	<.001	91/416	2.79	1.69–4.58	<.001
Change in ectopic burden								
Ref: Unchanged low VPC burden	11/200	1.00	1.00	NA	14/200	1.00	1.00	NA
Reduction in VPC burden	6/82	1.17	0.43–3.18	.761	6/82	1.08	0.42–2.82	.869
Increase in VPC burden	15/80	2.97	1.35–6.51	.007	13/80	2.32	1.09–4.97	.030
Unchanged high VPC burden	73/336	2.90	1.51–5.56	.001	78/336	2.99	1.66–5.37	<.001

CI, confidence intervals; VPC, ventricular premature complexes.

Cox proportional hazard regression model assessing the relative risk of the end points by ectopic burden.

Separate models were fitted for each end point. For the HF/death end point, we adjusted for diabetes, LBBB QRS morphology, gender, hospitalizations 1 year prior to enrollment, GFR≥60, and baseline LVESV indexed by BSA. For the end point of VT/VF, we adjusted for prior ventricular arrhythmias, QRS duration, gender, and LVESV indexed by body surface area.

We found no significant differences between patients who experienced increase in VPC burden and those who had an unchanged high VPC burden (HF/death: p = .937, VT/VF: p = .406).

Low VPC burden (≤10 VPCs/hour), high VPC burden (>10 VPCs/hour).

simple method for evaluating postimplantation ectopic burden that can be conducted in a wide variety of settings. The results from this study suggest that ectopic burden measured at 12 months after device implantation is valuable for estimating long-term prognosis in CRT-D patients with mild HF. Furthermore, the information provided by the Holter recordings may help guide clinicians with further treatment including pharmacological and/or radiofrequency ablation to reduce ectopic burden (Lakkireddy et al., 2012) and/or device programming modifications to potentially improve prognosis. However, the assessment of efficacy of such interventions was not the scope of this study, and thus further studies are needed to evaluate these aspects of patient management.

4.2 | Limitations

In the current study, we only included patients with a 12-month 24-hour Holter monitoring. We therefore exclude all patients who died prior to the 12-month follow-up, which could potentially create a survival bias. However, there were only 20 deaths in CRT-D patients during the first year, while we do not believe it would have had a significant effect on our results. Although we have tried to adjust for factors that could have affected our results, a risk of unmeasured confounding remains.

Lastly, in the MADIT-CRT trial, only patients randomized to CRT-D implantation received a 24-hour Holter monitoring; therefore, we are unable to evaluate the specific effects of CRT-D on changes in ectopic burden, since we do not have a comparisons group of ICD patients. Furthermore, it is difficult to establish whether the higher risk of the end points in the group with a high ectopy burden, is due to an ectopy-driven attenuated efficacy of the CRT-D device, or if the ectopy burden in itself contribute with independent risk.

5 | CONCLUSION

In CRT-D patients with preexisting ischemic or nonischemic cardiomyopathy and mild heart failure, high ectopic burden (>10 VPCs/hour) at 12-month follow-up was associated with a 24% and 25% 3-year risk of HF/death and VT/VF, respectively, and a threefold increased relative risk of the end points as compared to patients with a low burden (≤ 10 VPCs/hour). Ectopic burden at 12 months may be a valuable approach for evaluating prognosis, and may help identify patients with high ectopic burden that could benefit from appropriate treatment interventions to optimize CRT-D efficacy. However, further studies are needed to evaluate the potential efficacy of such interventions.
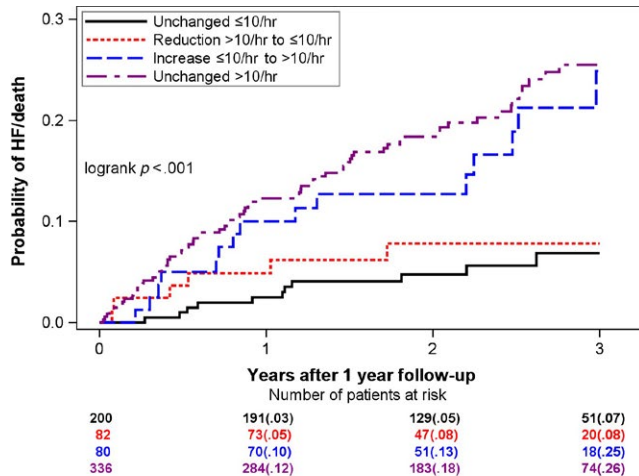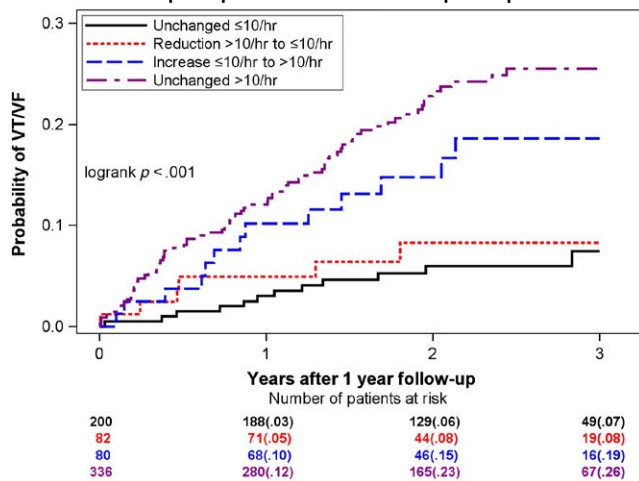
(a) Probability of HF/death by change in 24-hour Holter ectopic burden from preimplantation to 12 months postimplantation

(b) Probability of VT/VF by change in 24-hour Holter ectopic burden from preimplantation to 12 months potsimplantation

FIGURE 3 Probability of outcome by change in ectopic burden from preimplantation to 12-month postimplantation 24-hour Holter. Kaplan–Meier plots showing the probability of HF/death (a) and ventricular tachyarrhythmias (b) by four groups of changes in ventricular ectopic burden from preimplantation Holter to 12-month follow-up Holter. Ectopic burden was evaluated by 24-hour Holter monitoring prior to device implantation and at the 12-month follow-up visit. Low ectopic burden is defined as ≤ 10 ventricular ectopic beats per hour. High ectopic burden is defined as >10 ventricular ectopic beats per hour. Groups of change: Unchanged low burden (black): Patients who presented with both a low preimplantation and low 12-month ectopic burden. Reduced burden (red): Patients who presented with a high preimplantation ectopic burden and a low 12-month ectopic burden. Increased burden (blue): Patients who presented with a low ectopic burden preimplantation and a high ectopic burden at 12-month follow-up. Unchanged high burden (purple): Patients who presented with both a high preimplantation and high 12-month ectopic burden

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TABLE 3 Factors associated with low ectopic burden at 12 months

	Odds ratio	95% confidence interval	*p* Value
Female gender	2.29	1.58–3.32	<.001
BU ≤25 mg/dl	1.68	1.12–2.50	.012
QRS ≥150 ms	1.67	1.14–2.45	.008
Left bundle branch block	1.60	1.06–2.40	.025
Reduction in age by decade (10 years)	1.24	1.06–1.45	.009
Reduction in LVESV indexed by BSA (10 ml/m^2)	1.16	1.07–1.26	<.001

VPC, ventricular premature complexes; LVESV, left ventricular end systolic volume; BSA, body surface area; BUN, blood urea nitrogen.
Low ectopic burden, ≤10 VPCs/hour.

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