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Tachycardia Therapy Outcomes of Ischemic Versus Nonischemic Cardiomyopathy on Cardiac Resynchronization Therapy: A Propensity Score-matched Analysis

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Abstract

Objective: **This investigation aimed to investigate differences between dilated cardiomyopathy (DCM) and ischemic cardiomyopathy (ICM) patients treated with cardiac resynchronization therapy with defibrillator (CRT-D) for tachycardia therapy-related outcomes as well as mortality during follow-up of at least 1 year.**

Methods: **Seventy-eight patients with DCM (n = 42) and ICM (n = 36) with implantation or upgradation to CRT-D were included in this study and analyzed for incidence of non-sustained ventricular tachycardia (NSVT), non-sustained ventricular fibrillation (NSVF), defibrillator therapies, anti-tachycardia pacing (ATP), and mortality.**

Results: **DCM was the underlying etiology in 42 (53.84%) and ICM in 36 (46.15%). Time to first therapy was numerically longer in DCM than in ICM (9.5 ± 2.4 vs. 7.1 ± 3.2; P-value = 0.088). DCM patients had significantly higher therapy-free survival and mortality compared with ICM patients (OR (95%CI): 0.238 (0.155−0.424); log-rank P = 0.017) and (OR (95% CI): 0.612 (0.254−0.924); log-rank P = 0.029). ICM (HR (95%CI): 0.529 (0.243−0.925); P-value = 0.014) CAD (HR (95%CI): 0.326 (0.122−0.691): P-value = 0.003), and NSVT (HR (95%CI): 0.703 (0.513−0.849): P-value = 0.005) were demonstrated as independent predictors of the primary endpoint of appropriate therapy in CRT-D and ICM (HR (95%CI): 0.421 (0.321−0.524); P-value = 0.037), chronic kidney disease (CKD; HR (95%CI): 0.289 (0.198−0.380); P-value = 0.013), and CAD (HR (95%CI): 0.786 (0.531−0.967); P-value = 0.003) were predictors of mortality.**

Conclusion: **The clinical course of ICM and DCM cohorts who were treated with CRT-D differs significantly during follow-up, with increased tachycardia therapy and increased incidence of mortality in ICM patients.**

Keywords: Heart failure, Biventricular pacing, Implantable cardioverter defibrillator, Ischemic cardiomyopathy, Dilated cardiomyopathy

1. Introduction

In advanced heart failure (HF), QRS duration decreases all-cause mortality proportionally.[1] With the left bundle branch block (LBBB), there is a prolongation of QRS duration causing left ventricle (LV) activation delay via a transmural functional line of obstruction in the lateral wall and LV septum.[2] This results in ventricular dyssynchrony. The use of biventricular pacing in patients with drug-resistant HF and interventricular conduction delay can achieve optimization of cardiac performance.[3] For LV pacing, the electrodes are selectively inserted in cardiac veins through the coronary sinus and right ventricle (RV) pacing is achieved by transvenous lead insertion in the RV. The MIRACLE (Multicenter InSync Randomized Clinical Evaluation) study demonstrated clinical benefits of atrial-synchronized biventricular pacing in patients with New York Heart Association (NYHA) class III or

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ambulatory IV HF who had an LV ejection fraction (LVEF) of ≤35% with a QRS duration of 120 ms of more.[4] This method was named cardiac resynchronization therapy (CRT), and it became an established treatment for symptomatic HF with intraventricular conduction delay in the form of LBBB.[2]

The COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trial demonstrated a better prognosis in patients with CRT plus defibrillator (CRT-D) compared with guideline-directed medical therapy (GDMT) alone.[5] The analysis of the interaction between etiology and intervention was not significant. Similarly, in CARE-HF (Cardiac Resynchronization - Heart Failure) study, CRT had reduced mortality in ischemic and nonischemic cardiomyopathy (CM).[6] In addition, it decreases the risk of sudden cardiac death (SCD) due to ventricular tachycardia (VT) and ventricular fibrillation (VF) by an implantable cardioverter defibrillator (ICD).[7] A meta-analysis demonstrated a reduction in all-cause mortality pronounced in ischemic cardiomyopathy (ICM) compared to dilated cardiomyopathy (DCM).[8] Data on arrhythmic events and respective ICD therapy in CRT-D is scarce during moderate follow-up in South Asia. There we aimed to investigate differences between DCM and ICM patients treated with CRT-D for tachycardia therapy-related outcomes as well as mortality during follow-up of at least 1 year.

2. Methods

A total of 85 patients with HF were implanted with a CRT-D device at our institute from Jan 2012 to Dec 2022. This is a retrospective single-center study done at a tertiary care hospital in Pakistan. The study was approved by the hospital ethics committee (study ID #S/029/2022). Patient consent was waived off by the ethical committee due to the retrospective nature of the study and the anonymization of the patient data used in this investigation. All devices were implanted with the traditional selection criteria, including the NYHA functional class of III or ambulatory IV with GDMT, LVEF ≤35%, and QRS duration of ≥120 ms. Clinical status, including NYHA class, Minnesota quality-of-life score, and 6-min walk test (6-MWT) were taken from hospital records and by patient chart reviews. QRS duration was measured by baseline electrocardiograms (ECGs) using the widest QRS complex from leads II, V1, and V6. Echocardiography parameters were also obtained from patient charts and echocardiography department databases for LV volumes and LVEF at baseline and latest follow-up. Echocardiography response was defined as an improvement of ≥15% in LV end-systolic volume. To ensure long-term follow-up, only patients with CRT-D follow-up of at least 1-year were included in this study. This selection resulted in 78 patients with the first CRT-D implantation. Patients with irregular visits and no checkups in the last 3 months were also excluded. The primary endpoint was all-cause mortality and appropriate/inappropriate ATP or shock by ICD. ATP was defined as evidence of pacing on EGM after detection of any tachycardia episode by the device. Shock was defined as release of energy after failed ATP for tachycardia. To account for variable follow-up durations, the change in LVEF, total number of ATP for VT/VF, shocks for VT/VF and non-sustained VT/VF (NSVT/NSVF) were presented per 3 months.

Each follow-up is analyzed for any arrhythmia and ICD therapies (ATP or shock) starting with the initial visit post-implantation or upgrade. In patients with an upgradation from ICD, arrhythmia and device therapies before the upgrade were not included. To minimize interobserver bias, all device therapies and arrhythmia events were analyzed by two physicians (J.M. and M.A.). In case of doubt, electrograms were sent to the respective company. Appropriate therapy was defined as shock or ATP for VT or VF after analysis of the electrograms. NSVT and NSVF were defined as arrhythmia episodes in the respective programmed VT or VF zones.

All CRT-D device programming settings according to standard clinical care at our center were reviewed from patient charts. In general, two therapy zones (one VT and one VF) are programmed. If ATP therapy fails, VT is primarily treated with ATP and then with ICD shock. VE is mainly treated with ICD shock and ATP during charging. ICD programming is adapted according to the MADIT-RIT study: VT zone: cycle length 330−400 ms; detection: 24−28; re-detection: 12; VF zone: cycle length: 270−315 ms; detection 18−24; re-detection: 12 to 16.[9]

Descriptive data were presented as frequency (n) and percentages (%) for categorical variables and as mean and standard deviation (SD) for continuous variables. Baseline characteristics were compared using the Chi−Square test, Fisher's exact test for categorical variables, and Student's t-test for continuous variables (normally distributed). For normality of distribution, the Wilk−Shapiro test was used and abnormally distributed variables were analyzed with the Mann−Whitney U test. Matched categorical variables were presented as frequency and percentages and compared using McNazar's test. Matched continuous data were presented as

mean and SD and analyzed using Student's paired-samples t-test. Survival in groups was compared with the log-rank test. Univariate Cox regression analysis was performed to identify significant independent predictors of outcome. For multivariate analysis, significant predictors from the univariate analysis were included. The p-value <0.05 was considered statistically significant. All data were analyzed using the Statistical Package for Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA.).

3. Results

The study population consisted of 78 patients who were included in this study receiving DRT-D according to recommendations. DCM was the underlying etiology in 42 (53.84%) and ICM in 36 (46.15%). The mean age for these two groups was 67 ± 9.2 vs. 71 ± 8.5 (P-value = 0.012) and the mean LVEF was 25 ± 5% vs. 26 ± 8% (P-value = 0.195). Males were predominant in both groups 85.71% vs. 75% (P-value = 0.034). Baseline comorbidities and medications between the groups are presented in Table 1 after propensity score matching. Diabetes (P-value = 0.041), hypertension (P-value = 0.002), and chronic kidney disease (P-value = 0.003) were predominant in DCM while dyslipidemia (P-value = 0.036), coronary artery disease (P-value <0.001), prior MI (P-value <0.001), and stroke (P-value = 0.012) were more prevalent in patients with ICM. Quality of life score (P-value = 0.914) and 6-min walk test (P-value = 0.932) were non-significant between the two groups. QRS duration was only numerically higher in DCM patients (P-value = 0.735).

Table 1. Propensity score matched baseline characteristics. DCM (dilated cardiomyopathy); ICM (ischemic cardiomyopathy); LVEF (left ventricular ejection fraction); DM (diabetes mellitus); HTN (hypertension); PAD (peripheral arterial disease); CAD (coronary artery disease); MI (myocardial infarction); OSA (obstructive sleep apnea); AF (atrial fibrillation); SGLT (sodium-glucose cotransporter); NOAC (novel oral anticoagulants); NYHA (New York Heart Association); MWT (minute walk test); QOL (quality of life); LVEDV (left ventricular end-diastolic volume); LVESV (left ventricular end-systolic volume).

Variables	DCM (42)	ICM (36)	P-value
Age (yrs); mean ± SD	67 ± 9.2	71 ± 8.5	0.012
Male; n(%)	36 (85.71%)	27 (75%)	0.034
LVEF; n(%)	25 ± 5	26 ± 8	0.195
Comorids; n(%)			
DM	15 (35.71%)	11 (30.55%)	0.041
HTN	21 (50%)	14 (38.88%)	0.002
Dyslipidemia	16 (38.09%)	17 (47.22%)	0.036
PAD	7 (16.66%)	5 (13.88%)	0.106
CKD	27 (64.28%)	12 (33.33%)	0.003
Lung disease	7 (16.66%)	5 (13.88%)	0.112
CAD	9 (21.42%)	33 (91.66%)	<0.001
Prior MI	5 (11.9%)	27 (75%)	<0.001
Prior revascularization	2 (4.76%)	15 (41.66%)	<0.001
Prior stroke	2 (4.76%)	4 (11.11%)	0.012
OSA	5 (11.9%)	3 (8.33%)	0.097
AF	10 (23.8%)	7 (19.44%)	0.124
Prior medications; n(%)			
Sacubitril/Valsartan	34 (80.95%)	26 (72.22%)	0.523
SGLT-2 inhibitor	31 (73.8%)	25 (69.44%)	0.126
Aldosterone antagonist	21 (50%)	17 (47.22%)	0.932
Beta-blocker	26 (61.9%)	25 (69.44%)	0.471
Statin	25 (59.52%)	21 (58.33%)	0.994
Amiodarone	16 (38.09%)	5 (13.88%)	0.001
NOAC	13 (30.95%)	7 (19.44%)	0.026
Warfarin	8 (19.04%)	8 (22.22%)	0.956
NYHA at last follow-up; n(%)			
I	13 (30.95%)	12 (33.33%)	0.922
II	12 (28.57%)	11 (30.55%)	0.893
III	9 (21.42%)	7 (19.44%)	0.991
IV	8 (19.04%)	6 (16.66%)	0.750
6-MWT (m)	325 ± 107	321 ± 102	0.932
QOL score	30 ± 13	31 ± 9	0.914
QRS duration at last follow-up (ms)	112 ± 42	110 ± 56	0.735
LVEDV (ml)	216 ± 66	232 ± 57	0.149
LVESV (ml)	164 ± 67	168 ± 74	0.810

The mean time to first CRT-D implantation in DCM and ICM groups was 24 ± 12 vs. 22 ± 12 (P-value = 0.870) and the first CRT-D replacement was 13 ± 9 vs. 14 ± 10 (P-value = 0.120). Atrial pacing (AP; P-value = 0.801) and bi-ventricular pacing (BiVP; P-value = 0.911) rates were comparable between the 2 groups. All essential device-related characteristics are presented in Table 2. Appropriate shocks delivered in DCM and ICM groups for VT were 54.76% vs. 63.88% (P-value = 0.044) and VF was 7.14% vs. 13.88% (P-value = 0.074). Inappropriate shocks were more common in ICM as compared to DCM (61.11% vs. 35.71%; P-value <0.001). Time to first therapy was numerically longer in DCM than in ICM (9.5 ± 2.4 vs. 7.1 ± 3.2; P-value = 0.088). A detailed overview of ICD therapy is exhibited in Table 2. For the primary endpoint of therapy-free survival and mortality, DCM patients had significantly higher therapy-free survival and mortality compared with ICM patients (OR (95%CI): 0.238 (0.155−0.424); log-rank P = 0.017) and (OR (95%CI): 0.612 (0.254−0.924); log-rank P = 0.029) (Fig. 1).

Univariate Cox proportional analysis for appropriate CRT-D intervention (shock or ATP) revealed male gender, ICM, CAD, and NSVT to have a significant influence on the primary endpoint of appropriate CRT-D interventions. Furthermore, these were fitted as independent variables in a multivariate Cox proportional hazard model with CRT-D therapy as the independent variable. In this model, ICM (HR (95%CI): 0.529 (0.243−0.925); P-value = 0.014) CAD (HR (95%CI): 0.326 (0.122−0.691): P-value = 0.003), and NSVT (HR (95% CI): 0.703 (0.513−0.849): P-value = 0.005) were demonstrated as independent predictors of the primary endpoint of appropriate therapy in CRT-D. Predictors of mortality were ICM (HR (95%CI): 0.421 (0.321−0.524); P-value = 0.037), chronic kidney disease (CKD; HR (95%CI): 0.289 (0.198−0.380); P-value = 0.013), and CAD (HR (95%CI): 0.786 (0.531−0.967); P-value = 0.003) (Table 3).

4. Discussion

The present investigation evaluated the development of ventricular tachyarrhythmias and concomitant ICD therapy in patients after CRT-D implantation. The methodology was chosen to describe the “real world" follow-up of at least 1 year since no South Asian population has been studied for more than a few months. Data were analyzed between the 2 major etiologies of CM, including ICM and DCM, that cause HF with reduced EF (HFrEF); therefore, precipitating the implantation of CRT-D or ICD devices.

During the mean follow-up of 13 months, ICM patients exhibited numerically early time to first therapy when compared with DCM (7.1 ± 3.2 vs. 9.5 ± 2.4; P-value = 0.088) and 38.09% of patients with DCM while 22.22% with ICM were free of therapy throughout the follow-up for this investigation. Kaplan−Meier survival analysis demonstrated a significantly higher rate of CRT-D therapy in ICM patients. This was driven mainly by the higher rate of ATP during tachycardia. To date, several investigations have reported similar rates of tachycardia therapy in CRT-D patients when comparing DCM and ICM.[10,11] The post-hoc analysis of the MADIT-CRT (Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy) study reported the prevalence of first VT/VF of 27% in ICD and 22% in CRT-D patients after 40 months follow-up.[12] In our investigation, we observed a higher rate of tachycardia

Table 2. Propensity score matched device-related characteristics. DCM (dilated cardiomyopathy); ICM (ischemic cardiomyopathy); ICD (implantable cardioverter defibrillator); CRT (cardiac resynchronization therapy); AP (atrial pacing); BiVP (biventricular pacing); NSVT (non-sustained ventricular tachycardia); NSVF (non-sustained ventricular fibrillation); ATP (anti-tachycardia pacing).

Variables	DCM (n = 42)	ICM (n = 36)	P-value
Time to first CRT-D implant (months)	24 ± 12	22 ± 12	0.870
Time to first CRT-D replacement (months)	13 ± 9	14 ± 10	0.120
Upgrade to CRT-D; n(%)			
ICD	11 (26.19%)	7 (19.44%)	0.127
CRT-P	15 (35.71%)	12 (33.33%)	0.943
PPM	16 (38.09%)	17 (47.22%)	0.102
AP rate at last follow-up (%)	11.54 ± 6.12	12.09 ± 5.11	0.801
BiVP rate at last follow-up (%)	98.17 ± 1.04	97 ± 1.23	0.911
NSVT; n(%)	25 (59.52%)	23 (63.88%)	0.146
NSVF; n(%)	3 (7.14%)	5 (13.88%)	0.078
Appropriate ATP or shocks; n(%)			
VT	23 (54.76%)	23 (63.88%)	0.044
VF	3 (7.14%)	5 (13.88%)	0.074
Inappropriate ATP or shocks; n(%)	15 (35.71%)	22 (61.11%)	<0.001
Time to first therapy (months)	9.5 ± 2.4	7.1 ± 3.2	<0.001

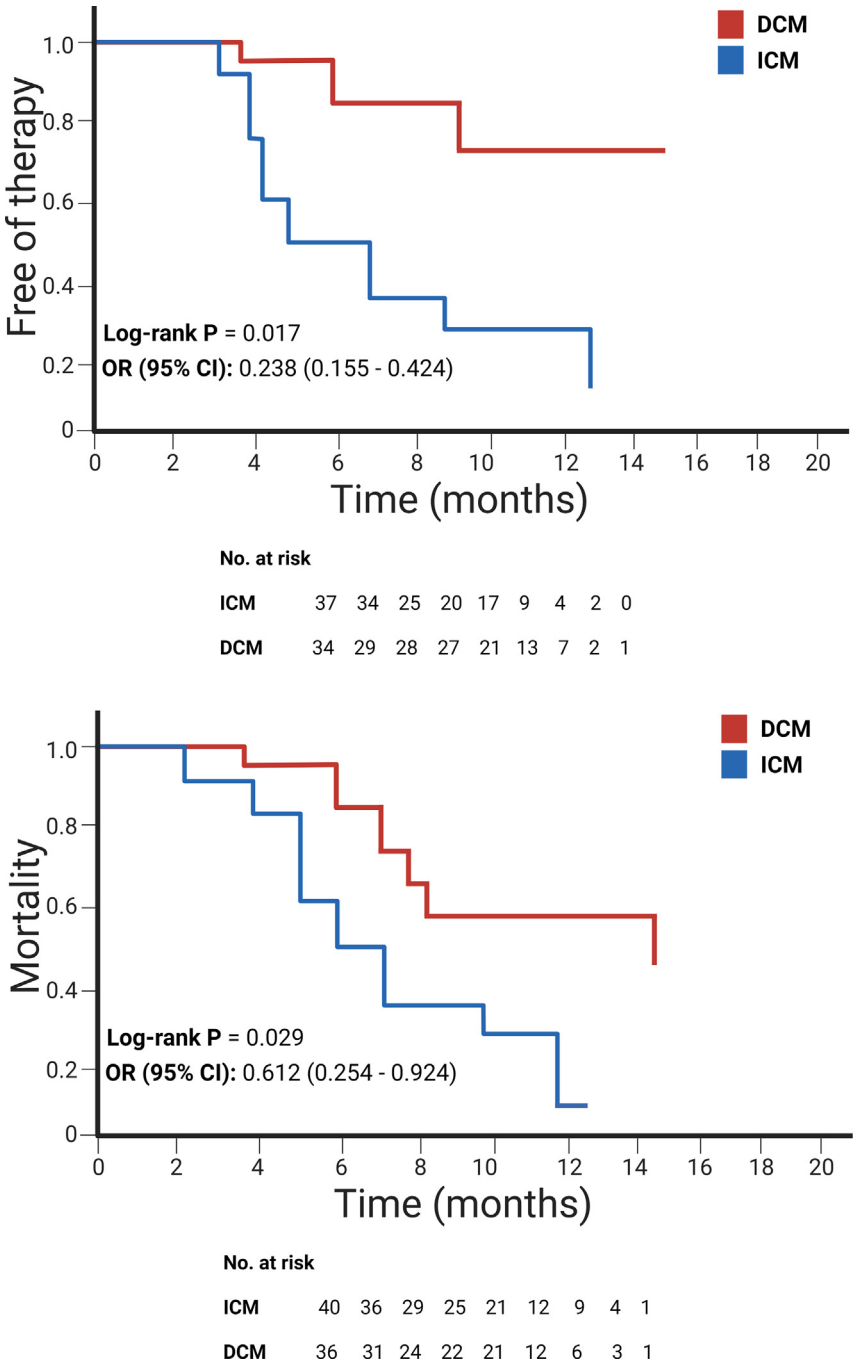

Fig. 1. Kaplan–Meier estimates of ICD therapy-free survival and cumulative survival in patients with CRT-D.

therapy in DCM (61.09%) and ICM (77.77%) groups. In another study consisting of 1544 patients, 13% experienced inappropriate shocks at a cumulative event rate of 7% for 1 year.[13] This is not similar to our inappropriate shock incidence of 35.71% and 61.11% in DCM and ICM, respectively. Because of arrhythmogenic myocardium is ICM, more tachycardia therapy was initiated in this patient cohort representing our investigation. One study reported an annual incidence of ICD shock at 10% in ICM and 4% in DCM.[14] Similarly, some previous investigations have reported numerically higher shock rates in ICM patients when compared with DCM patients, but their follow-up duration does not exceed 1 year and mainly only ICD devices were analyzed for shock therapies. Our study adds a year-long extra longitudinal observation and additional data on ATP. Therefore, the combination of

Table 3. Predictors by univariate and multivariate Cox proportional hazard ratios.

Variables	Univariate		Multivariate	
	HR (95%CI)	P-value	HR (95%CI)	P-value
Appropriate CRT-D intervention (shock or ATP)				
Age	1.034 (0.842–1.210)	0.436		
Male	0.755 (0.352–0.951)	0.025	1.328 (0.518–5.237)	0.154
ICM	2.170 (1.041–4.382)	0.032	0.529 (0.243–0.925)	0.014
Lung disease	0.321 (0.161–1.067)	0.822		
DM	1.033 (0.262–2.863)	0.064		
CKD	0.868 (0.404–1.065)	0.137		
CAD	0.442 (0.418–0.513)	0.001	0.326 (0.122–0.691)	0.003
NSVT	0.713 (0.462–0.782)	0.001	0.703 (0.513–0.849)	0.005
LVEF	1.256 (0.579–2.729)	0.460		
Mortality				
Age	1.316 (1.040–1.871)	0.447		
Male	3.753 (1.223–11.364)	0.256		
ICM	0.812 (0.543–0.965)	0.003	0.421 (0.321–0.524)	0.037
DM	1.212 (0.376–4.523)	0.349		
CKD	0.443 (0.223–0.651)	0.039	0.289 (0.198–0.380)	0.013
CAD	0.868 (0.645–1.167)	0.021	0.786 (0.531–0.967)	0.003
LVEF	0.664 (0.274–0.860)	0.001	0.379 (0.155–0.630)	0.024
PAD	0.852 (0.790–0.940)	0.037	3.889 (1.598–9.460)	0.617
NSVT	0.868 (0.645–1.167)	0.246		

both shock and ATP as the endpoint might explain the higher incidence of shock therapies in our patient cohort, and produce a statistically significant difference between ICM and DCM patients in terms of VT shocks. Myocardial scarring has different patterns in both patient populations, with predominantly endocardial scarring in ICM vs. more isolated mid-myocardial or epicardial scars in DCM patients. It has been demonstrated that type of myocardial scarring has an impact on the occurrence of arrhythmia.[15] Therefore, different patterns of scar formation can lead to differential arrhythmia rates and ICD interventions.

In addition to increased ICD interventions, our investigation demonstrated a significant increase in mortality in patients suffering from ICM compared to DCM patients. At present, there are conflicting data available on mortality comparing both CMs treated with CRT-D. One study shows a decreased all-cause mortality in the ICM group.[7] Another study exhibited no statistical difference in mortality between the two groups.[16] One other study shows mortality benefits among DCM patients.[17] The DANISH (Danish ICD Study in Patients with Dilated Cardiomyopathy) trial reported no benefit of CRT-D in terms of mortality in patients with HF without CAD.[18] In the same trial, more than 50% of the population was treated with CRT-D or CRT-P devices. In our investigation, there was an increased risk of ICD therapy and increased mortality in ICM patients. The excess mortality might be due to a higher rate of comorbid conditions. Peripheral arterial disease (PAD), and CKD share a risk profile similar to CAD, and the rates of CAD and prior myocardial infarction were numerically higher in ICM patients. Even in our small population, these differences were significant and multivariate analysis identified CKD as an independent predictor of mortality in our patient cohort. This is in line with previous studies, demonstrating increased mortality with CAD, PAD, and CKD.[19,20] We identified NSVT, CAD, and ICM as independent predictors of tachycardia therapy and ICM, CKD, CAD, and LVEF as predictors of mortality in this cohort. Similarly, it was demonstrated in the MADIT-CRT trial that each 5% LVEF was associated with a 30% reduction in the risk of VT/VF.[12]

5. Limitations

In addition to the limitations of the retrospective study design, our small study population had its limitations. Differences in device programming setups might have influenced the rates of shock or ATP in patients with ICM and DCM. We reported a "real-world" non-selected patient cohort during GDMT. all devices were programmed according to the latest recommendations at the respective point in time. A prospective multi-center study including a large sample size would be useful in assessing the outcomes of tachycardia therapy after CRT-D implantation.

6. Conclusion

In conclusion, this investigation demonstrates a variable rate of arrhythmic events, subsequent ICD

interventions, and mortality depending upon the underlying etiology of CM. Patients with ICM had more device therapies during follow-up and a higher incidence of inappropriate shock or ATP along with a higher risk of death. LVED before device implantation, CAD, presence of ICM, NSVT, and CKD were the strongest predictors of mortality.

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Conflicts of interest

The authors have no conflict of interests to declare.

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