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Time Dependence of Ventricular Tachyarrhythmias After Myocardial Infarction

A MADIT-CRT Substudy

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ABSTRACT

OBJECTIVES The purpose of this study was to assess the relationship between the time since a myocardial infarction (MI) and the risk of ventricular tachyarrhythmic events (VTEs) in patients with left ventricular dysfunction and mild symptoms of heart failure.

BACKGROUND Patients with left ventricular dysfunction after MI are at high risk for VTEs.

METHODS Ventricular tachycardia (VT), ventricular fibrillation (VF), or death as a function of time since MI was assessed in 693 patients enrolled in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy). Patients were categorized as those with a period of <3 years since an MI (lowest quartile, n = 172) versus those with a period of ≥3 years since an MI (n = 521). Risk of VT/VF or death was compared.

RESULTS Cumulative probability of VT/VF or death was significantly higher among patients in the highest quartile of time since an MI compared with those in the lowest quartile (41% vs. 22%, p = 0.015). Multivariate analysis showed that in patients with left bundle branch block (LBBB), those with a period of ≥3 years since an MI had a significantly higher risk of VT/VF or death (hazard ratio: 2.33; 95% confidence interval: 1.43 to 3.80; p = 0.001) and a higher risk of VT/VF (hazard ratio: 3.18; 95% confidence interval: 1.71 to 5.90; p < 0.001) compared with patients with a period of <3 years since an MI. These findings were consistent when the time since an MI was analyzed in a continuous fashion. A significant relationship between the time since an MI and outcomes was not observed in patients with non-LBBB.

CONCLUSIONS Among post-MI patients with left ventricular dysfunction and LBBB, the risk of VTEs is directly related to the time since an MI occurred. (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy [MADIT-CRT]; NCT00180271) (J Am Coll Cardiol EP 2016;2:565–73) © 2016 by the American College of Cardiology Foundation.

An important marker of mortality in the post-myocardial infarction (MI) period is the presence of left ventricular dysfunction (1,2). Patients with left ventricular dysfunction after MI are at high risk for ventricular tachyarrhythmias, resulting in death (3,4). Early restoration of coronary perfusion (5), together with treatment with beta-blockers (6) and angiotensin-converting enzyme inhibitors (7) has resulted in significant reductions in death in post-MI patients. However, the formation of myocardial fibrosis and dense scar can become the pathological substrate for the development of ventricular arrhythmias, particularly in the setting of left ventricular dysfunction. Adverse remodeling, scar tissue formation, transient ischemia, left ventricular dilatation, and the onset of heart failure are some of the factors that may trigger and maintain ventricular tachyarrhythmias (1,8).

Implantable cardioverter-defibrillators (ICDs) implanted 40 days after MI and 90 days after revascularization reduce the risk of sudden death in post-MI patients with left ventricular dysfunction (4,9–11). However, in post-MI patients, the apparent benefit of ICD implantation has been shown to be greatest after 18 months (12); however, in other studies, a time dependency has not been observed (13).

Therefore, the present study was performed to explore the relationship between the time since an MI and the risk of ventricular tachyarrhythmic events (VTEs) in patients with left ventricular dysfunction and mild symptoms of heart failure who were

enrolled in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy) trial (14).

METHODS

STUDY POPULATION. The design and results from MADIT-CRT have previously been published (14,15). For this study, we performed a post hoc analysis of the primary data collected in MADIT-CRT. Briefly, 1,820 patients enrolled at 110 hospitals in the United States, Canada, and Europe were randomized in a 3:2 ratio to receive CRT with a defibrillator (CRT-D) or an ICD. Patients of either sex who were at least 21 years of age were enrolled if they had ischemic cardiomyopathy (New York Heart Association [NYHA] functional class I or II) or nonischemic cardiomyopathy (NYHA functional class II only), normal sinus rhythm, a left ventricular ejection fraction of ≤30%, and a QRS duration of ≥130 ms.

Of the 1,820 patients enrolled in the trial, 1,046 patients had ischemic cardiomyopathy, 693 of whom had documented previous MI with a known date of the MI. The remaining 353 patients with ischemic cardiomyopathy were excluded either due to documented coronary artery disease without documented MI (n = 237) or due to insufficient data regarding the presence and/or date of MI (n = 116). The study patients were diagnosed with ischemic cardiomyopathy if they had ≥1 of the following: 1) a documented (Q-wave or elevated cardiac biomarkers) MI; 2) a history of any revascularization procedure (either coronary artery bypass grafting [CABG] or percutaneous coronary intervention [PCI]); and 3) documented significant coronary stenosis by coronary angiography and signs or symptoms related to coronary stenosis. The time since the MI was defined as the time from the date of the most recent MI to device implantation. We categorized patients by quartiles of the time since the MI and then compared quartile 1 patients with patients in quartiles 2 to 4. Quartile 1 included patients with a period of <3 years since the MI (n = 172) and quartiles 2 to 4 included (n = 521) patients with a period of ≥3 years since the MI.

DEVICE PROGRAMMING AND INTERROGATION. Commercially available defibrillators (Boston Scientific, Natick, Massachusetts) and standard implantation techniques were used in MADIT-CRT. Device programming and interrogation were performed as described previously (15). CRT-D and ICDs were programmed for monitoring and therapy; sensitivity was programmed according to physician decisions. The trial recommended a setting of the VT detection zone starting at 180 beats/min and the VF detection zone at 210 beats/min. A detection delay of 2.5 s for the VT zone and 1.0 s for the VF zone was recommended. The protocol suggested programming the VT zone first therapy to burst-type antitachycardia pacing with 8 pulses at 88% of the measured cycle length with a 10-ms decrement between bursts, and then shock therapy.

All devices were interrogated quarterly and after any ICD shock therapies. All device interrogations and arrhythmia episodes were adjudicated in a core laboratory. The definition of VT in this particular analysis was from 180 beats/min (recommended programming) up to 250 beats/min using the stored electrograms of the episode, if the rate of the ventricular electrograms (V) was greater than the rate of the atrial electrograms (A), and if there was a 1:1 atrioventricular conduction V-V changes that drove A-A changes. VF was defined as a ventricular rate >250 beats/min with disorganized ventricular electrograms. In this analysis, only appropriate therapy delivered for VT or VF was considered. The analysis was performed on an intention-to-treat basis.

DEFINITIONS AND ENDPOINTS. The primary endpoint of the present study was the first occurrence of appropriate ICD therapy for VT/VF or death. Secondary endpoints included the following events: appropriate device therapy for the combined endpoint of VT/VF, appropriate antitachycardia pacing therapy alone, and appropriate device shock therapy.

STATISTICAL ANALYSIS. Baseline characteristics of the study patients with a period of <3 years and a period of ≥3 years since an MI were compared with the Wilcoxon rank-sum test or chi-square test as appropriate. The cumulative probabilities of VT/VF or death by the time since an MI were displayed according to the Kaplan-Meier method for both groups, with comparison of cumulative event rates assessed by the log-rank test. Multivariate Cox proportional hazards regression modeling was used to estimate the adjusted risk for the different endpoints by the period of <3 years since an MI versus the period of ≥3 years since an MI and by the time an MI analyzed as a continuous variable (per 10-year increments). The best subsets regression approach was used to identify potential variables to be included in the multivariate regression model; only those that were significant at $p < 0.05$ were included in the final model. Multivariate analysis was performed separately for patients

ABBREVIATIONS AND ACRONYMS

CRT-D = cardiac resynchronization therapy with defibrillator

ICD = implantable cardioverter-defibrillator

LBBB = left bundle branch block

MI = myocardial infarction

NYHA = New York Heart Association

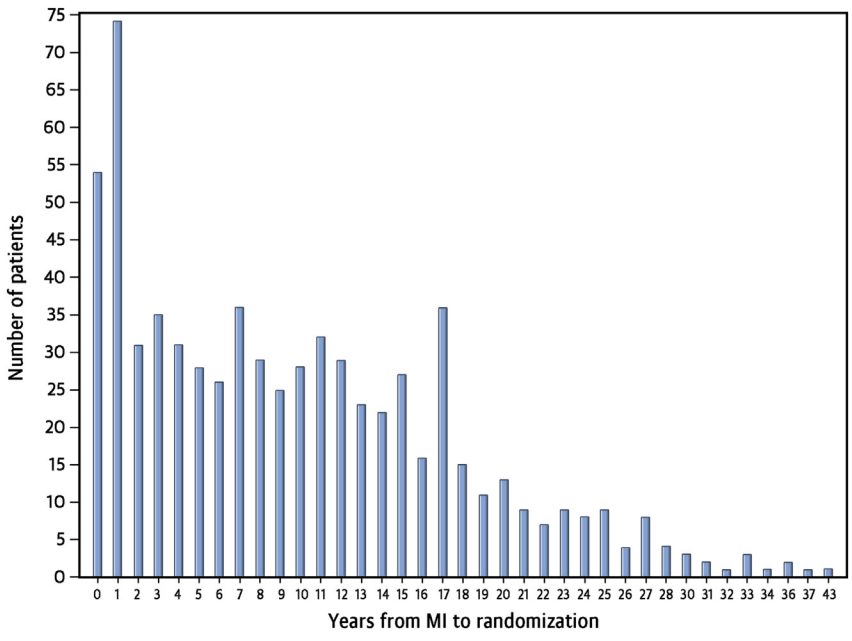
PCI = percutaneous coronary intervention

VF = ventricular fibrillation

VT = ventricular tachycardia

VTE = ventricular tachyarrhythmic event

FIGURE 1 Distribution of Time Between MI and Randomization to Defibrillator Implantation



MI = myocardial infarction.

with left bundle branch block (LBBB) and those with non-LBBB. Covariates included in the multivariate regression model were treatment with CRT-D, age at enrollment, blood urea nitrogen, left ventricular end-diastolic volume index, current smoking status, history of revascularization, and history of ventricular arrhythmias. The proportional hazards assumption for the Cox regression model was tested using interactions between variables and follow-up time. All p values were 2-tailed, and a p value of <0.05 was considered statistically significant. The association of time since an MI with the risk of outcome among ICD only patients and among CRT-D patients was assessed by including a CRT-D treatment-by-time since an MI interaction with the multivariate models. Analyses were performed using version 6.0 of the MADIT-CRT database, with the extended follow-up (endpoints collected until September 2010) using SAS software (version 9.4, SAS Institute, Cary, North Carolina).

RESULTS

PATIENT CHARACTERISTICS. The median time from the MI to enrollment in the trial was 8.6 years (interquartile range: 12.1 years). The primary endpoint of VT/VF or death occurred in 256 (37%) patients during a median follow-up time of 3.3 years (interquartile range: 1.5 years).

Figure 1 shows the distribution of time since the MI to enrollment in the trial. Of the 693 patients with previous MIs, 521 (75%) had their MIs ≥3 years before enrollment. Baseline characteristics of the study patients according to the time since the MI are listed in Table 1. Patients with a period of ≥3 years since an MI were older and were less likely to have diabetes mellitus and hypertension compared with patients with a period of <3 years since an MI. Patients with a period of ≥3 years since an MI were more likely to have undergone coronary artery bypass grafting compared with patients with a period of <3 years since an MI. Treatment assignment to a CRT-D device was lower in patients with a period of ≥3 years since an MI compared with those with a period of <3 years since an MI. The mean left ventricular ejection fraction, QRS duration, body mass index, and glomerular filtration rate were similar between the 2 groups. Most patients in each group were on beta-blocker therapy, angiotensin-converting enzyme inhibitors or aldosterone receptor blockers, and statin drugs. In patients with LBBB, the median left ventricular ejection fraction was 28.7% versus 29.5% for patients with non-LBBB ($p < 0.001$).

TIME SINCE MI AND RISK OF VTE. The cumulative probability for the primary endpoint of VT/VF or death by quartiles of time since an MI is shown in Figure 2. The cumulative probability of VT/VF or death at 3 years was 41% in the highest quartile and 22% in the lowest quartile ($p = 0.015$ for the overall difference). Similarly, a significantly higher cumulative probability of VT/VF was seen in patients in the highest quartile of time since an MI compared with patients in the lowest quartile of time since an MI ($p < 0.001$) (Figure 3).

Among MI patients with LBBB, multivariate analysis showed that patients with a period of ≥3 years since an MI had a significant 2.3-fold (95% confidence interval: 1.43 to 3.80; $p = 0.001$) higher risk of VT/VF or death compared with those with a period of <3 years since an MI and a similar higher risk for the secondary endpoints (Table 2). In LBBB patients, a significant and increasing risk for adverse outcomes was observed with an increasing time since an MI, which was analyzed as a continuous variable (Table 2). Among patients with LBBB, there were no significant differences between the effect of time since an MI on outcomes among ICD and CRT-D patients (all treatment-by-time since an MI interaction p value of >0.05) (Table 2).

In the subgroup of MI patients with non-LBBB, no significant relationships were observed between the time since an MI and the different endpoints (Table 3). Among non-LBBB patients, although significant treatment interactions were observed, the p values for the different endpoints were insignificant.

TABLE 1 Baseline Characteristics of Patients With Elapsed Time From MI <3 and ≥3 Years

	Time From MI <3 yrs (n = 172)	Time From MI ≥3 yrs (n = 521)	p Value
Age, yrs	65.1 ± 9.8	67.3 ± 9.0	0.011
Female	25 (15)	59 (11)	0.263
Diabetes mellitus	74 (44)	159 (31)	0.002
Hypertension	129 (75)	342 (66)	0.024
Previous PCI	106 (62)	242 (46)	<0.001
Previous CABG	73 (42)	311 (60)	<0.001
Systolic blood pressure, mm Hg	123 ± 18	122.0 ± 18	0.793
Currently smoking, %	28 (16)	64 (12)	0.186
Body mass index, kg/m^2	29.0 ± 4.8	28.5 ± 5.0	0.265
NYHA functional class II	129 (75)	369 (71)	0.291
Left bundle branch block	100 (58)	267 (51)	0.116
QRS duration, ms	152 ± 16	153 ± 18	0.813
Glomerular filtration rate, ml/min/1.73 m^2	67 ± 20	66 ± 20	0.585
Left ventricular ejection fraction, %	29 ± 3	29 ± 3	0.844
Left atrial volume index, ml/BSA	46 ± 9	47 ± 11	0.112
Left ventricular end-systolic volume index	83 ± 18	86 ± 20	0.070
Beta-blockers	160 (93)	478 (92)	0.591
ACE inhibitors/ARB	160 (93)	490 (94)	0.628
Statins	153 (89)	460 (88)	0.814
Antiarrhythmic drug therapy	16 (9)	63 (12)	0.318
CRT-D therapy	115 (67)	304 (58)	0.048
Past ventricular arrhythmias	15 (9)	57 (11)	0.404

Values are mean ± SD or n (%). A p value of <0.05 was considered statistically significant.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BSA = body surface area; CABG = coronary artery bypass grafting; CRT-D = cardiac resynchronization therapy-defibrillator; MI = myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

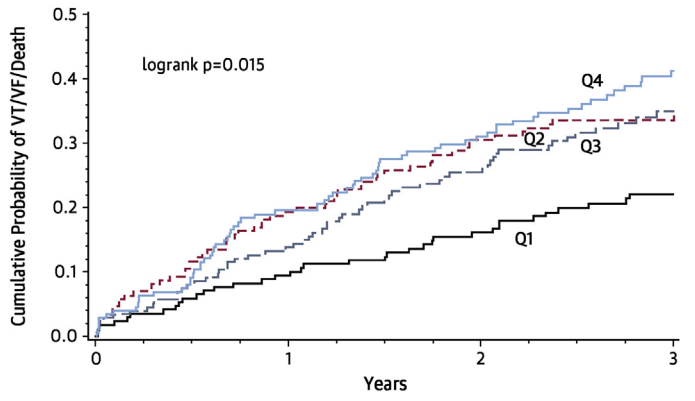
DISCUSSION

The present study demonstrated that in patients with ischemic cardiomyopathy and mild symptoms of heart failure, those with a period of ≥3 years since an MI had a significantly higher risk of ventricular tachyarrhythmias or death compared with those with a period of <3 years since an MI. These results were consistent when the time since an MI was evaluated as a continuous variable. These findings were most striking in those with LBBB. These results suggest that there is a positive relationship between the time since an MI and the risk of ventricular tachyarrhythmias; as the time since an MI increases, particularly in those with a LBBB, the risk of ventricular tachyarrhythmias also increases. This finding was consistent in both the ICD only group and in the CRT-D group of patients with LBBB. A significant relationship between the time since an MI and adverse outcomes was not observed in the non-LBBB group of patients.

There are several causes of ventricular tachyarrhythmias and sudden cardiac death in the post-MI period. The extent and duration of myocardial ischemia and the adequacy of coronary reperfusion are important determinants of the development and progression of myocardial scar and left ventricular dilatation and dysfunction (16,17). Cellular, neurohormonal, and ion channel changes during the post-MI period can result in adverse cardiac remodeling that predispose such patients to VT and VF (18–23). The aforementioned factors are constantly at play and do not diminish over time, which is likely the reason why in our analysis of a higher risk of VTEs was observed in patients with longer times since an MI occurred.

In the MADIT-II (Multicenter Automatic Defibrillator Implantation-II Trial), a time-dependent increase in the risk of all-cause mortality was observed in patients with longer times since an MI (defined

FIGURE 2 Kaplan-Meier Estimates of the Cumulative Probability of VT/VF or Death by 4 Quartiles of Elapsed Time From Myocardial Infarction

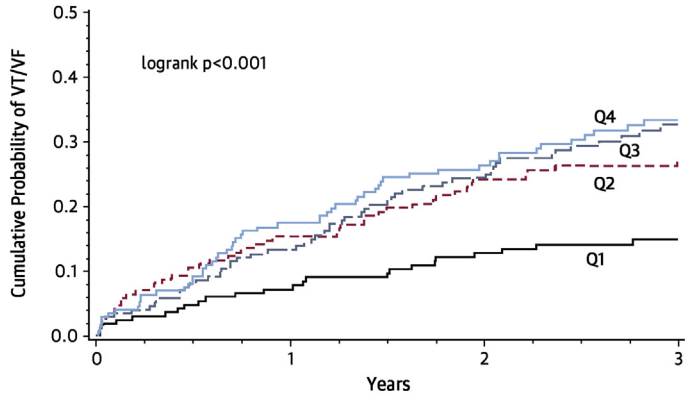


Patients at Risk			
Q1 172	152 (0.09)	137 (0.16)	90 (0.22)
Q2 172	137 (0.19)	116 (0.31)	83 (0.34)
Q3 175	148 (0.14)	124 (0.25)	69 (0.35)
Q4 174	140 (0.20)	115 (0.31)	71 (0.41)

VT/VF = ventricular tachycardia/ventricular fibrillation.

as ≥18 months) compared with patients with a more recent MI (defined as <18 months) (12). However, in the MADIT-II subanalysis, the time since an MI as a continuous variable was not assessed, and endpoints like VT/VF and appropriate ICD therapies were not reported. Similarly, an analysis from the SEARCH MI (Survey to Evaluate Arrhythmia Rate in High-risk MI) registry showed that the cumulative incidence of VTEs and appropriate device shock or antitachycardia pacing were significantly higher in patients with a longer time since an MI (24). The findings of our study are consistent with the findings of these 2 studies, indicating that the survival benefit from an ICD or CRT-D are recognized in the long term and that patients with longer time since an MIs should not be considered to be at low risk for adverse outcomes.

FIGURE 3 Kaplan-Meier Estimates of the Cumulative Probability of VT/VF by All 4 Quartiles of Elapsed Time From Myocardial Infarction



Patients at Risk			
Q1 172	152 (0.07)	137 (0.13)	90 (0.15)
Q2 172	137 (0.15)	116 (0.24)	83 (0.27)
Q3 175	148 (0.13)	124 (0.24)	69 (0.33)
Q4 174	140 (0.17)	115 (0.26)	71 (0.33)

Abbreviation as in Figure 2.

However, an analysis from the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) study among 712 patients with an MI showed no difference in mortality or sudden cardiac death as a function of time since an MI (13). However, appropriate ICD shocks were more common in SCD-HeFT patients with a longer time since an MI. The disparities observed between our study and the SCD-HeFT analysis might be due to important differences in the patient population and in ICD programming.

Although the risk of ventricular tachyarrhythmias is high early after MI (1,2,25), studies of ICD implantation in the early post-MI period have failed to show a significant mortality benefit (26,27); therefore, current device guidelines provide clear recommendations as to when an ICD should be implanted after an MI and after coronary revascularization (28). Although an ICD reduces the risk of sudden death in the early post-MI period, the competing risks of nonsudden and noncardiac death during this time frame far outweighs the potential benefit that can be realized with an ICD (26,27). In this time period, the use of the wearable cardioverter defibrillator is a viable alternative to reduce sudden cardiac death (29,30). However, the true impact of an ICD on survival of post-MI patients becomes evident in the long-term, as demonstrated in our study.

Among patients with MI enrolled in MADIT-CRT, the risk of VTEs was found to be highest among patients without previous coronary revascularization (31). Among those who underwent coronary revascularization, a risk reduction in VT/VF or death was related to the time since any revascularization procedure (31). To account for the effect of coronary revascularization, we adjusted for any coronary revascularization and for time since coronary revascularization and found consistent results, which showed a direct relationship between the time since an MI and the risk of VTEs.

STUDY LIMITATIONS. Our study had several limitations that require attention. MADIT-CRT enrolled patients with NYHA functional class I and II heart failure symptoms, and the findings of higher risk for VTEs with increasing time since an MI might not apply to patients with NYHA functional class III or IV

TABLE 2 Multivariate Analysis in Patients With Myocardial Infarction and Left Bundle Branch Block

	Time After MI ≥3 yrs vs. Time After MI <3 yrs				Time After MI as Continuous Variable (HR for Every 10-yr Increment)			
Treatment Arm	HR	95% CI	p Value	Interaction p Value	HR	95% CI	p Value	Interaction p Value
VT/VF/death (117 events)								
Combined	2.33	1.43–3.80	0.001		1.30	1.036–1.64	0.024	
ICD	2.58	1.24–5.38	0.011		1.35	0.985–1.85	0.062	
CRT-D	2.14	1.13–4.06	0.019	0.703	1.26	0.912–1.74	0.161	0.761
VT/VF (89 events)								
Combined	3.18	1.71–5.90	<0.001		1.44	1.107–1.87	0.007	
ICD	3.54	1.36–9.21	0.01		1.52	1.061–2.18	0.022	
CRT-D	2.94	1.33–6.47	0.008	0.763	1.36	0.947–1.96	0.096	0.661
ATP (63 events)								
Combined	3.03	1.45–6.32	0.003		1.53	1.116–2.10	0.008	
ICD	2.80	0.96–8.19	0.06		1.67	1.074–2.58	0.023	
CRT-D	3.22	1.21–8.59	0.02	0.847	1.41	0.904–2.18	0.130	0.584
Shock (51 events)								
Combined	2.98	1.30–6.84	0.01		1.47	1.033–2.08	0.032	
ICD	3.50	1.02–11.99	0.046		1.43	0.913–2.23	0.118	
CRT-D	2.59	0.86–7.79	0.091	0.716	1.52	0.911–2.55	0.109	0.844

Risk of ventricular tachyarrhythmic events and implantable cardioverter-defibrillator (ICD) therapy for patients with myocardial infarction (MI) and LBBB. Hazard ratios (HR) reported by a period of ≥3 years since an MI compared with patients with a period of <3 years since an MI and by time since an MI analyzed as a continuous variable. Adjusted for treatment with cardiac resynchronization therapy (CRT), age at enrollment, blood urea nitrogen, left ventricular end diastolic volume index, history of revascularization, history of ventricular arrhythmias, and current smoking.

ATP = antitachycardia pacing; CI = confidence interval; VF = ventricular fibrillation; VT = ventricular tachycardia.

TABLE 3 Multivariate Analysis in Patients With Myocardial Infarction and Non-Left Bundle Branch Block

	Time After MI ≥3 yrs vs. Time After MI <3 yrs				Time After MI as Continuous Variable (HR for Every 10-yr Increment)			
Treatment Arm	HR	95% CI	p Value	Interaction p Value	HR	95% CI	p Value	Interaction p Value
VT/VF/death (129 events)								
Combined	1.16	0.74–1.82	0.52		1.14	0.914–1.42	0.248	
ICD	0.61	0.31–1.21	0.159		1.05	0.726–1.52	0.800	
CRT-D	1.65	0.92–2.96	0.095	0.030	1.19	0.913–1.55	0.200	0.578
VT/VF (102 events)								
Combined	1.44	0.85–2.46	0.18		1.27	0.989–1.62	0.061	
ICD	0.60	0.29–1.23	0.164		1.04	0.679–1.58	0.866	
CRT-D	2.77	1.25–6.13	0.012	0.005	1.40	1.045–1.87	0.024	0.238
ATP (74 events)								
Combined	1.96	1.22–3.16	0.006		1.26	0.943–1.69	0.118	
ICD	0.54	0.22–1.23	0.141		0.85	0.511–1.40	0.519	
CRT-D	3.34	1.18–9.41	0.023	0.007	1.55	1.104–2.19	0.012	0.042
Shock (57 events)								
Combined	1.11	0.55–2.24	0.762		1.22	0.872–1.70	0.246	
ICD	0.60	0.22–1.65	0.318		1.49	0.829–2.69	0.181	
CRT-D	1.69	0.64–4.42	0.288	0.145	1.13	0.762–1.67	0.548	0.421

Risk of ventricular tachyarrhythmic events and ICD therapy for patients with MI and non-left bundle branch block. HRs reported by a period of ≥3 years since an MI compared with patients with a period of <3 years since an MI and by time since an MI analyzed as a continuous variable. Adjusted for treatment with CRT, age at enrollment, blood urea nitrogen, left ventricular end-diastolic volume index, history of revascularization, history of ventricular arrhythmias, and current smoking.

Abbreviations as in Table 2.

symptoms. In addition, there was an extensive variable imbalance between the 2 groups that might affect the results; however, multivariable analysis showed consistent results for the multiple endpoints analyzed, suggesting that there was a time-dependent relationship between the time since an MI and the risk of VTEs. Finally, silent MIs and myocardial injury resulting in troponin leaks might have introduced bias to our results.

CONCLUSIONS

In this study, we found a strong association between the elapsed time since an MI and the risk for VTEs among post-MI patients with left ventricular dysfunction and LBBB who were implanted with an ICD or CRT-D. The risk for VTEs was higher in patients with LBBB and a period of ≥3 years since an MI compared with those with a period of <3 years since an MI. These findings suggest that patients with longer times since MIs should be closely monitored and considered for implantation of an ICD or CRT-D when indicated, to reduce the risk of sudden cardiac death and improve outcomes.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: An increasing time since an MI is associated with higher risk of ventricular tachyarrhythmias among patients with mild to moderate heart failure and left bundle branch block who are treated with an ICD or CRT-D.

TRANSLATIONAL OUTLOOK: Left ventricular dysfunction is a known risk factor for the development of ventricular arrhythmias. However, there is a need to better risk stratify patients at risk for sudden death. The time since an MI occurred may be used as an additional marker of risk and should be studied further in patients with ischemic cardiomyopathy.

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KEY WORDS cardiac resynchronization therapy, implantable cardioverter-defibrillators, myocardial infarction, ventricular fibrillation, ventricular tachycardia

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