Clinical features and predictors of lethal ventricular tachyarrhythmias after cardiac resynchronization therapy for primary prevention of sudden cardiac death

（心臓再同期療法後に生ずる致死性心室性不整脈の臨床像とその予測因子に関する検討）

申請者

弘前大学大学院医学研究科

循環病態科学領域循環病態内科学教育分野

氏名　　石田　祐司

指導教授　奥村　謙

ABSTRACT

Background: Cardiac resynchronization therapy (CRT) reduces the mortality rate among patients with advanced heart failure (HF) and a wide QRS complex. Despite such clinical improvement, the clinical features of ventricular tachyarrhythmias (VA) and the risk of sudden cardiac death (SCD) among these patients still remain to be elucidated.

Methods: In total, 128 consecutive patients with advanced HF (mean age, 68 ± 10 years; 90 men; mean left ventricular ejection fraction [LVEF], 27% ± 7%) who underwent CRT with a cardioverter-defibrillator (CRT-D) as the primary prevention for SCD were examined. Twenty-nine patients had ischemic cardiomyopathy (ICM), whereas the other 99 patients had nonischemic cardiomyopathy (NICM). At each follow-up examination, patient- and device-related data were collected. All detected VA episodes were analyzed.

Results: During a mean period of 1,009 ± 566 days, 30 patients (23%) experienced appropriate cardioverter-defibrillator treatment for sustained VA. Twenty-six had NICM and the other 4 had ICM. The first VA episodes mostly involved monomorphic ventricular tachycardia (VT) at 187 ± 30 beats/minute (28 patients, 93%). The mode of successful therapy was antitachycardia pacing (ATP) in 60% of patients. Multiple linear regression analysis revealed that among clinically plausible predictors (age; gender; LVEF; underlying rhythms; QRS duration; QT interval; ischemic cause of HF; history of nonsustained VT; and the uses of amiodarone, β-blockers, and renin-angiotensin inhibitors), only the history of nonsustained VT ($P < 0.0001$) was a significant predictor of appropriate cardioverter-defibrillator therapy.

Conclusions: After implantation of a CRT-D device for primary prevention, VAs were more prone to occur in patients with nonischemic HF than in those with ischemic HF. Moreover, the first VA episodes were mostly monomorphic VT, and most episodes were terminated by ATP. In addition, nonsustained VT was a potent predictor of VA after CRT.

1. INTRODUCTION

Intraventricular conduction disturbance and atrioventricular, intraventricular, and interventricular dyssynchrony are likely to occur in severe heart failure (HF), and the vital prognosis worsens as dyssynchrony progresses and the QRS width increases [1-3]. Cardiac resynchronization therapy (CRT) improves hemodynamics by improving dyssynchrony and increasing the efficiency of cardiac contraction, leading to improvement in the patient's quality of life (QOL) and vital prognosis [4].

In the CArdiac REsynchronization-Heart Failure (CARE-HF) study [5, 6], CRT with a pacemaker (CRT-P) was found to decrease the incidence of deaths from all causes and HF, and inhibited sudden cardiac death in patients with HF, compared with optimal pharmacological therapy, demonstrating the effect of CRT on the vital prognosis of patients with HF. The subjects of this study had advanced HF with New York Heart Association (NYHA) classes III and IV, and these outcomes may have been indicative of implantable cardioverter-defibrillator (ICD) for the primary prevention of sudden cardiac death by ventricular tachyarrhythmias (VAs). However, the proarrhythmic effect of CRT itself has been problematic-that is, the heterogeneity of transmural repolarization from the left ventricular epicardial to endocardial sides is increased by left ventricular epicardial pacing after CRT, and the JT and T_{peak}-T_{end} intervals prolong the QT interval, resulting in the occurrence of VAs [7]. A subanalysis of the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) study [8] revealed a 56% reduction in the risk of sudden cardiac death in patients who underwent CRT with a defibrillator (CRT-D) compared with those who underwent pharmacological therapy, which was associated with appropriate defibrillator discharge for ventricular tachycardia (VT) and ventricular fibrillation (VF) in 11.6% at 1 year and 19.3% at 2 years. No predictive factors of lethal VAs occurring after CRT have been established, and the Guidelines for Non-Pharmacotherapy of Cardiac Arrhythmias [9] recommend CRT-D for NYHA class III or IV patients with left ventricular ejection fraction (LVEF) of ≤35%, wide QRS of ≥120 ms, and indications for ICD. However, the role of CRT-D in the primary prevention of sudden cardiac death in Japanese patients with advanced HF has not been fully understood.

In the present study, we investigated the incidence of VAs occurring after CRT-D device implantation and analyzed in detail all the arrhythmic episodes in patients with advanced HF who underwent CRT-D for the primary prevention of sudden cardiac death. In addition, we investigated the clinical features and predictive factors of VAs occurring after CRT-D.

2. MATERIALS AND METHODS

2.1. Study population

This study included 128 consecutive patients with advanced HF complicated by intraventricular conduction disturbance. All patients underwent CRT-D device implantation for HF and as the primary prevention of sudden cardiac death between August 2006 and July 2012 at Hirosaki University Hospital. There were 90 men and 38 women, and their mean age was 68 ± 10 years (Table 1). The underlying disease was coronary artery disease in 29 patients (23%), dilated cardiomyopathy in 77 patients (60%), hypertrophic cardiomyopathy in 9 patients (7%), and sarcoidosis and other diseases in 4 patients (3%). LVEF, measured by using left ventriculography, was 27% ± 7.1% for all patients. None of the patients had previous episodes of sustained VT or VF; however, 52 patients (44%) had nonsustained VT (NSVT). β-Blockers were administered in 109 patients (85%), angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB) were administered in 96 patients (76%), and amiodarone was administered in 35 patients (27%). The CRT-D device was implanted according to the Guidelines for Non-Pharmacotherapy of Cardiac Arrhythmias issued by the Japanese Circulation Society [9]. This study was approved by the medical ethics committee of our institution (approved date was July 18th, 2013, approval number 2013-127).

2.2. Follow-up and device interrogation

The CRT-D device used was the Protecta XT CRT-D (Medtronic, Inc., Minneapolis, Minnesota) in 18 patients; the Consulta CRT-D (Medtronic, Inc.) in 23 patients; the Concerto (Medtronic, Inc.) in 22 patients; the InSync III Marquis (Medtronic, Inc.) in 3 patients; the CONTAK (Guidant, Inc., St. Paul, Minnesota) in 34 patients; the COGNIS (Boston Scientific, Natick, Massachusetts) in 22 patients; the INCEPTA (Boston Scientific) in 1 patient; the Promote (St. Jude Medical, St. Paul, Minnesota) in 3 patients; the ATLAS+HF (St. Jude Medical) in 1 patient; and the Unify (St. Jude Medical) in 1 patient.

After implantation of the CRT-D device, all patients visited the outpatient clinic periodically or the device clinic every 3-6 months for follow-up examination, and device-related data were collected at these instances. Thirty-one patients (24%) used a remote monitoring system: the CareLink Network (Medtronic Inc.) was used in 25 patients; the LATITUDE Patient Management System (Boston Scientific) was used in 5 patients; and the Marlin.net Patient Care Network (St. Jude Medical) was used in the remaining patient. In these patients, the data were collected using the remote

monitoring systems through automatic monthly transmission. Device-related data were also collected when patients unexpectedly visited the outpatient clinic for symptomatic arrhythmic episodes and HF symptoms. All VA events collected from the devices were analyzed. Appropriate and inappropriate therapies were differentiated through the assessment of intracardiac electrocardiograms, collected from the devices, by several cardiologists. Moreover, we analyzed the VA episodes to determine the type of detected VA using the intracardiac electrocardiogram of the device. We distinguished between monomorphic VT and polymorphic VT or VF by the regularity and morphology of the tachycardia.

2.3. End point and statistical analysis

The end point of this observational study was the first occurrence of appropriate therapies. Most of the devices were programmed with their default settings.

All data are shown as mean ± one standard deviation. For comparison of the baseline characteristics, the t-test or analysis of variance (ANOVA) was used for continuous variables, and the χ^2 test was used for nominal variables. To investigate the predictors for appropriate defibrillator therapy, the univariate analysis was performed using the following variables: age; gender; LVEF; presence of ischemia; underlying rhythm; QRS width and QT time before CRT-D device implantation; past history of NSVT; and presence of amiodarone, β-blocker, ACE-I, or ARB medication. A final model was prepared with selected variables with $P < 0.10$, and multivariate analysis was performed using the Cox proportional hazard model. A P value of <0.05 was regarded as significant in all tests. All statistical analyses were performed using the JMP 9 Pro (SAS Institute Inc., Cary, North Carolina).

3. RESULTS

3.1. Incidence of VAs after CRT-D device implantation

During a follow-up period of 1,009 ± 566 days (range, 45-2,661 days), appropriate CRT-D therapy for VAs was observed in 30 patients (23%) (Figure 1). Table 2 shows the comparison of clinical characteristics between the 2 groups with (n = 30) and without appropriate ICD therapy (n = 98). Of the 30 patients with appropriate ICD therapy, 26 (87%) had nonischemic cardiomyopathy(NICM) and the other 4 had ischemic cardiomyopathy (ICM). Although the nonischemic origin was more prevalent in patients with ICD therapy (87%) than in those without therapy (74%), the difference was not statistically significant ($P = 0.1688$). The incidence of NSVT was significantly higher in the group with appropriate ICD therapy (70%) than in the group without therapy (30%) ($P < 0.0001$).

3.2. Type of first VA episode after CRT-D and mode of successful therapy

The median time from CRT-D implantation to the first appropriate therapy was 496 ± 94 days (range, 20-1951 days). As shown in Figure 2, intracardiac electrocardiogram analysis of the device demonstrated that the first VA episode was monomorphic VT in 28 patients (93%), whereas the other 2 patients (7%) had polymorphic VT or VF. The mean rate of monomorphic VT was 187 ± 30 beats/minute. The mode of successful therapy was antitachycardia pacing (ATP) in 60% of patients. In the other 40% of patients, ATP was ineffective and the VA was terminated by shock therapy.

3.3. Predictors of appropriate ICD therapy

As shown in Table 3, the univariate analysis using the Cox proportional hazard model demonstrated that QRS duration ($P = 0.085$), previous history of NSVT ($P < 0.001$), and ACE-I/ARB medication ($P = 0.085$) were significant variables. The multivariate analysis using the Cox proportional hazard model after adjusting for age and gender revealed that only a previous history of NSVT was an independent predictor of appropriate CRT-D therapy ($P < 0.001$). In 20 patients, the heart rate of NSVT before CRT-D device implantation could be analyzed, and was found to be 153 ± 22 beats/minute. The rate of sustained VT after CRT-D device implantation in these patients was 190 ± 36 beats/minute and was significantly higher than that of NSVT before implantation ($P = 0.0011$).

3.4. Impact of NSVT prior to CRT-D on the occurrence of sustained VA and prognosis

As shown in Figure 3, appropriate ICD therapy was observed in 23 of the 52 patients (44%) with a previous history of NSVT. In contrast, only 7 of the 76 patients (9%) without a history of NSVT experienced ICD therapy (Log rank test, $P < 0.0001$). The all-cause mortality was 49% (17/35) in the patients with a previous history of NSVT, whereas it was only 9% (6/70) in those without a history of NSVT. When the all-cause mortality was compared between patients with and without appropriate ICD therapy, the morality rate was 50% (15/30) in those with ICD therapy and 8% (8/98) in those without ICD therapy (Log rank test, $P < 0.0001$).

4. DISCUSSION

By analyzing the device data in patients with advanced HF implanted with CRT-D for primary prevention of sudden cardiac death, we found that: 23% of the patients experienced appropriate CRT-D therapy during a mean follow-up duration of 34 months; many of the first VA episodes involved monomorphic VT and were treated by ATP; and NSVT was a potent predictor of sustained VAs occurring after CRT-D.

4.1. Incidence of the first VA episode after CRT-D as primary prevention of sudden cardiac death

In patients who underwent CRT-D, particularly those undergoing this treatment for primary prevention of sudden cardiac death, the rate of appropriate ICD therapy for VA was reported to be 21% at 21 months (12%/year) after implantation in the study by Soliman et al. [10], 15% at 16 months (11.3%/year) in the COMPANION trial [8], and 21% at 18 months (14%/year) in the study by Ypenburg et al. [11] In the present analysis, appropriate ICD therapy was observed in 30 of 128 consecutive patients (23%) during the 34-month period (8.1%/year), showing a similar rate to or slightly lower rate than those reported previously [8, 10, 11], despite the fact that the present study had a much higher number of patients with NICM than those in previous studies [8, 10, 11]. Of the patients experiencing appropriate ICD therapy after implantation in the present study, 26 patients (87%) had NICM as the underlying disease, whereas only 4 (13%) had ICM. This was related to the characteristics of the patients in the present study-NICM was noted among 77% of the patients in the present study, which was much higher than that noted in Caucasian studies (45% in MADIT-CRT [12]). Previous Japanese cohort studies [13, 14] demonstrated that the vital prognosis of Japanese patients with myocardial infarction was favorable, and the rate of sudden cardiac death was low compared with those in the MADIT-II study [15]. Iles et al. [16] reported that patients with NICM and myocardial fibrosis, detected by late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMRI), had an ICD therapy rate that was as high as that among patients with ICM; however, the patients in both of these groups exhibited a significantly higher risk than those without LGE on CMRI-that is, as the disease advances, the risk of ICD therapy increases.

4.2. Clinical features and predictors of VA after CRT

Soliman et al. [10] reported that NSVT detected before CRT is an independent predictor of appropriate defibrillator therapy. Our results in Japanese patients were consistent with previous findings, and multivariate analysis demonstrated that NSVT detected before CRT-D device implantation was an independent predictor of VA appearing after CRT-D. However, although several previous studies [8, 10] reported that reduced LVEF and QRS width were also predictors, we found no predictive significance in these indices. A recent study from Manfredi et al. [17] demonstrated that in patients with a primary prevention indication for CRT-D, the estimated 2-year risk of appropriate ICD therapy is 3.3%, 2.5%, and 1.9% for a post-CRT-D LVEF of 45%, 50%, and 55%, respectively. When a CRT responder demonstrates near normalization in LVEF to ≥45%,

the incidence of ICD therapy for VA becomes low. The observation period was longer in our study (mean, 34 months) than in the others, and patients who showed improved or aggravated LVEF compared with that at the time of implantation may have been included in our study, both of which may have influenced our analysis. In addition, favorable narrower QRS might have been obtained with improved dyssynchrony after CRT-D in some patients. Thus, the QRS width did not seem to be a significant predictor in the present study. NSVT, as an independent predictor, indicates the presence of arrhythmogenic substrate before CRT-D device implantation.

VA episodes occurring after CRT-D mostly involved monomorphic VT, and more than half of the episodes could be terminated by ATP before shock therapy, suggesting that the mechanism of the present VA involves reentry occurring in the arrhythmogenic substrate that was already present before CRT-D. At the same time, approximately half of the monomorphic VT occurring for the first time after CRT-D failed to be terminated by ATP. We believe that there are several reasons for this failure of termination. First, it may be related to the mechanism of VT. Theoretically, ATP is considered to be effective for almost all cases of reentrant tachycardia [18-21]. Thus, it was possible that the mechanism of some monomorphic VT involved enhanced automaticity and not reentry. Second, it may have been influenced by the ICD setting. Although the first VA episode after CRT-D device implantation involved reentrant VT, it was possible that ATP was not able to capture the tachycardia, which could be treated if the ICD was set to have increased pacing or shorter pacing intervals.

ICD is generally programmed only for VF treatment in cases of primary prevention. Since the VA episodes detected mostly involved sustained monomorphic VT in the present analysis, we believe that ATP should be programmed in the device setting for CRT-D, which is performed for primary prevention of sudden cardiac death, especially in patients with NICM, as evidenced in the present study.

4.3. Study limitations

This is a retrospective, observational study performed at a single institution. Since the end point was appropriate ICD therapy, it is possible that because of the device treatment setting, an overtreatment with ATP or shock therapy by the device might have been applied to self-terminating VA. The presence or absence of NSVT before CRT-D was estimated by 24-hour Holter monitoring before CRT-D implantation, and therefore, false-negative cases for NSVT may be present in our cohort.

5. CONCLUSIONS

Appropriate ICD therapy for VA occurred in approximately 20% of patients with advanced HF during the 34-month follow-up period after CRT-D device implantation for the primary prevention of sudden cardiac death, and the rate of the therapy increased with time. The first VA episodes after CRT mostly involved monomorphic VT, and most episodes were terminated by ATP, indicating the necessity of ATP in the setting of the device. Finally, NSVT was a significant predictor of the appropriate ICD therapy after CRT-D. Moreover, aggressive drug therapy including β-blockers and amiodarone would be helpful in such patients.

Disclosures: None

Figure Legends

Figure 1. Kaplan-Meier estimate of the time to first appropriate ventricular tachycardia (VT)/ventricular fibrillation (VF) therapy in the primary prevention of sudden cardiac death. ICD = implantable cardioverter-defibrillator.

Figure 2. Clinical features of the first appearing ventricular tachyarrhythmias after cardiac resynchronization therapy (Panel A) and the mode of successful therapy (Panel B). VT = ventricular tachycardia; VF = ventricular fibrillation; ATP = antitachycardia pacing.

Figure 3. Impact of nonsustained ventricular tachycardia (NSVT) before cardiac resynchronization therapy on the occurrence of sustained ventricular tachyarrhythmias (VA) (Panel A) and all-cause mortality (Panel B). VT = ventricular tachycardia; VF = ventricular fibrillation.

References

[1] Baldasseroni S, Opasich C, Gorini M, et al. Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian network on congestive heart failure. Am Heart J 2002;143:398-405

[2] Grines CL, Bashore TM, Boudoulas H, et al. Functional abnormalities in isolated left bundle branch block. The effect of interventricular asynchrony. Circulation 1989;79:845-53

[3] Murkofsky RL, Dangas G, Diamond JA, et al. A prolonged QRS duration on surface electrocardiogram is a specific indicator of left ventricular dysfunction [see comment]. J Am Coll Cardiol 1998;32:476-82

[4] Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140-50

[5] Cleland JG, Daubert JC, Erdmann E, et al. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CArdiac REsynchronization-Heart Failure (CARE-HF) trial extension phase]. Eur Heart J 2006;27:1928-32

[6] Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539-49

[7] Medina-Ravell VA, Lankipalli RS, Yan GX, et al. Effect of epicardial or biventricular pacing to prolong QT interval and increase transmural dispersion of repolarization: does resynchronization therapy pose a risk for patients predisposed to long QT or torsade de pointes? Circulation 2003;107:740-6

[8] Saxon LA, Bristow MR, Boehmer J, et al. Predictors of sudden cardiac death and appropriate shock in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Trial. Circulation 2006;114:2766-72

[9] Okumura K, Yoshifusa A, Aonuma K, et al. Guidelines for non-pharmacotherapy of cardiac arrhythmias. JCS2011. [In Japanese]. Available from: ⟨http://www.j-circ.or.jp/guideline/pdf/JCS2011_okumura_h.pdf⟩ [accessed06.08.13].

[10] Soliman OI, Theuns DA, van Dalen BM, et al. Prediction of appropriate defibrillator therapy in heart failure patients treated with cardiac resynchronization therapy. Am J Cardiol 2010;105:105-11

[11] Ypenburg C, van Erven L, Bleeker GB, et al. Benefit of combined resynchronization and defibrillator therapy in heart failure patients with and without ventricular

arrhythmias. J Am Coll Cardiol 2006;48:464-70
[12] Barsheshet A, Goldenberg I, Moss AJ, et al. Response to preventive cardiac resynchronization therapy in patients with ischaemic and nonischaemic cardiomyopathy in MADIT-CRT. Eur Heart J 2011;32:1622-30
[13] Shiga T, Hagiwara N, Ogawa H, et al. Sudden cardiac death and left ventricular ejection fraction during long-term follow-up after acute myocardial infarction in the primary percutaneous coronary intervention era: results from the HIJAMI-II registry. Heart 2009;95:216-20
[14] Tanno K, Miyoshi F, Watanabe N, et al. Are the MADIT II criteria for ICD implantation appropriate for Japanese patients? Circ J 2005;69:19-22
[15] Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877-83
[16] Iles L, Pfluger H, Lefkovits L, et al. Myocardial fibrosis predicts appropriate device therapy in patients with implantable cardioverter-defibrillators for primary prevention of sudden cardiac death. J Am Coll Cardiol 2011;57:821-8
[17] Manfredi JA, Al-Khatib SM, Shaw LK, et al. Association between left ventricular ejection fraction post-cardiac resynchronization treatment and subsequent implantable cardioverter defibrillator therapy for sustained ventricular tachyarrhythmias. Circ Arrhythm Electrophysiol 2013;6:257-64
[18] Wathen MS, Sweeney MO, DeGroot PJ, et al. Shock reduction using antitachycardia pacing for spontaneous rapid ventricular tachycardia in patients with coronary artery disease. Circulation 2001;104:796-801
[19] Wathen MS, DeGroot PJ, Sweeney MO, et al. Prospective randomized multicenter trial of empirical antitachycardia pacing versus shocks for spontaneous rapid ventricular tachycardia in patients with implantable cardioverter-defibrillators: Pacing Fast Ventricular Tachycardia Reduces Shock Therapies (PainFREE Rx II) trial results. Circulation 2004;110:2591-96
[20] Wilkoff BL, Stern R, Williamson B, et al. Design of the Primary Prevention Parameters Evaluation (PREPARE) trial of implantable cardioverter defibrillators to reduce patient morbidity [NCT00279279]. Trials 2006;7:18
[21] Wilkoff BL, Williamson BD, Stern RS, et al. Strategic programming of detection and therapy parameters in implantable cardioverter-defibrillators reduces shocks in primary prevention patients: results from the PREPARE (Primary Prevention Parameters Evaluation) study. J Am Coll Cardiol 2008;52:541-50

Table 1. Clinical characteristics of the study patients

Variable	Total Population (n = 128)
Age (year)	67±10
Male gender	90 (70%)
ICM / NICM	29/99
Prevalence of NICM	77%
LVEF (%)	27±7.1
Chronic AF rhythm	37 (29%)
QRS duration (msec)	162±26
QT interval (msec)	449±50
History of NSVT	52 (41%)
Medication	
Amiodarone	35 (27%)
β-blocker	109 (85%)
ACE-I/ARB	97 (76%)

ICM = ischemic cardiomyopathy; NICM = non ischemic cardiomyopathy; LVEF = left ventricular ejection fraction; AF = atrial fibrillation; NSVT = non sustained ventricular tachycardia; ACE-I=angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker.

Table 2. Comparison of clinical characteristics between the patients with and without appropriate ICD therapy

Variable	Appropriate ICD therapy (n=30)	No appropriate ICD therapy (n=98)	P-value
Age (year)	65±10	68±10	0.1080
Male gender	22 (73%)	68 (69%)	0.6790
ICM / NICM	4/26	25/73	0.1633
Prevalence of NICM	87%	74%	0.1633
LVEF (%)	26±6.6	27±7.1	0.3321
Chronic AF rhythm	11 (37%)	26 (27%)	0.2839
QRS duration (msec)	155±28	164±25	0.0876
QT interval (msec)	444±58	450±48	0.5379
History of NSVT	23 (77%)	29 (30%)	<0.0001
Medication			
Amiodarone	10 (33%)	25 (26%)	0.4003
β-blocker	24 (80%)	85 (87%)	0.3640
ACE-I/ARB	26 (87%)	71 (73%)	0.1290

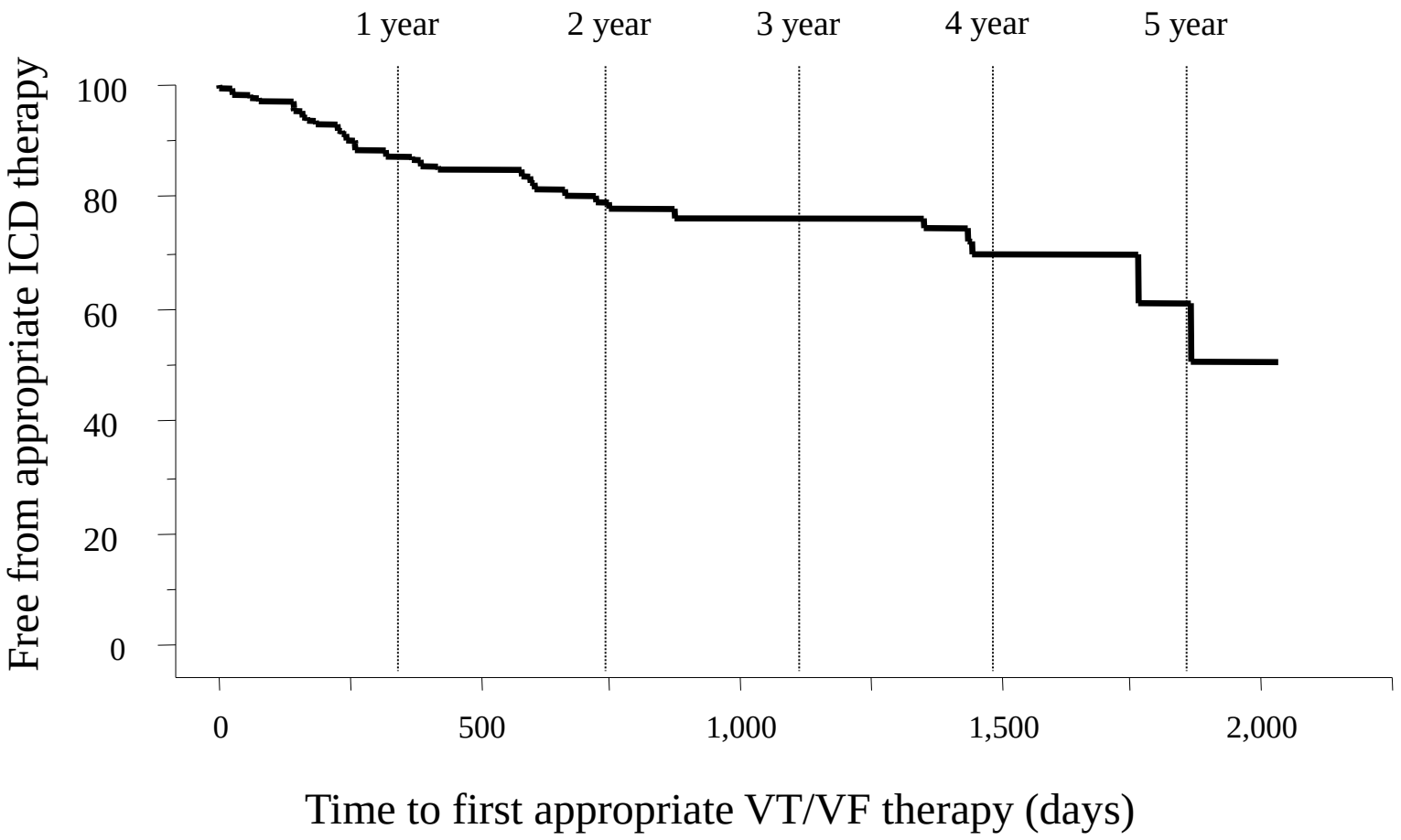
ICM = ischemic cardiomyopathy; NICM = non ischemic cardiomyopathy; LVEF = left ventricular ejection fraction; AF = atrial fibrillation; NSVT = non sustained ventricular tachycardia; ACE-I=angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker.

Table 3. Cox proportional hazard regression analysis of clinical parameters: predictor of ventricular tachyarrythmias

	Univariate Analysis			Multivariate Analysis		
Variable	HR	95%CI	P-value	HR	95%CI	P-value
Age (year)	0.9832	0.9576-1.0171	0.2643			
Male gender	1.2189	0.5635-2.9228	0.6261			
NICM	1.8966	0.7374-6.4348	0.1992			
LVEF (%)	0.9710	0.9230-1.0195	0.2401			
Chronic AF rhythm	1.6731	0.7693-3.4628	0.1867			
QRS duration (msec)	0.9875	0.9735-1.0017	0.0846	0.9914	0.9764-1.0064	0.2589
QT interval (msec)	0.9986	0.9910-1.0060	0.7128			
History of NSVT	5.2247	2.3570-13.1790	<0.0001	5.2879	2.3724-13.3927	<0.0001
Amiodarone	1.3534	0.6070-2.8282	0.4435			
β-blocker	0.5826	0.2527-1.5783	0.2650			
ACE-I/ARB	2.3208	0.8981-7.899	0.0858	2.5379	0.9700-8.7112	0.0586

ICM = ischemic cardiomyopathy; NICM = non ischemic cardiomyopathy; LVEF = left ventricular ejection fraction; AF = atrial fibrillation; NSVT = non sustained ventricular tachycardia; ACE-I=angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker.; HR = hazard ratio; CI = confidence interval.

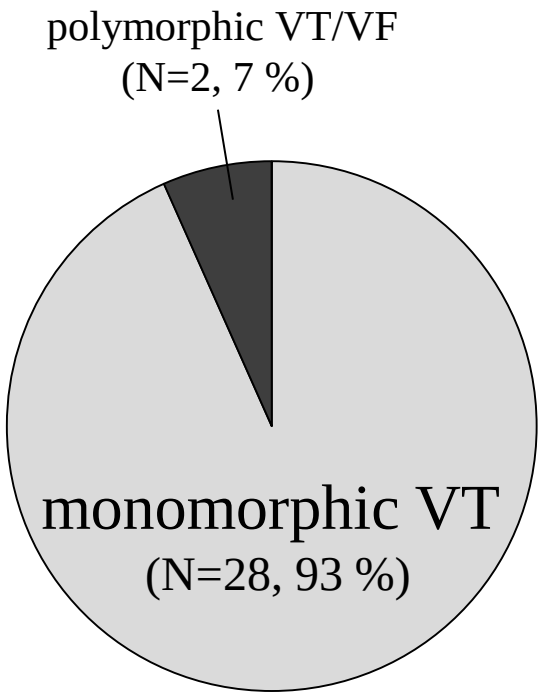
Figure 1



Cumulative annual risk for appropriate VT/VF therapy	1 year	2 year	3 year	4 year	5 year
	0.87	0.80	0.76	0.70	0.61

Figure 2

A Type of detected ventricular tachyarrhythmias



B Mode of successful therapy

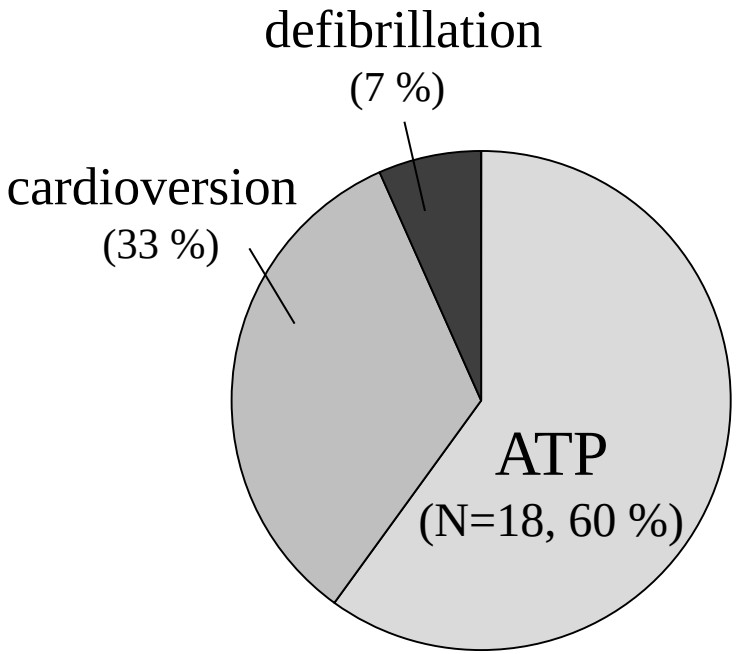
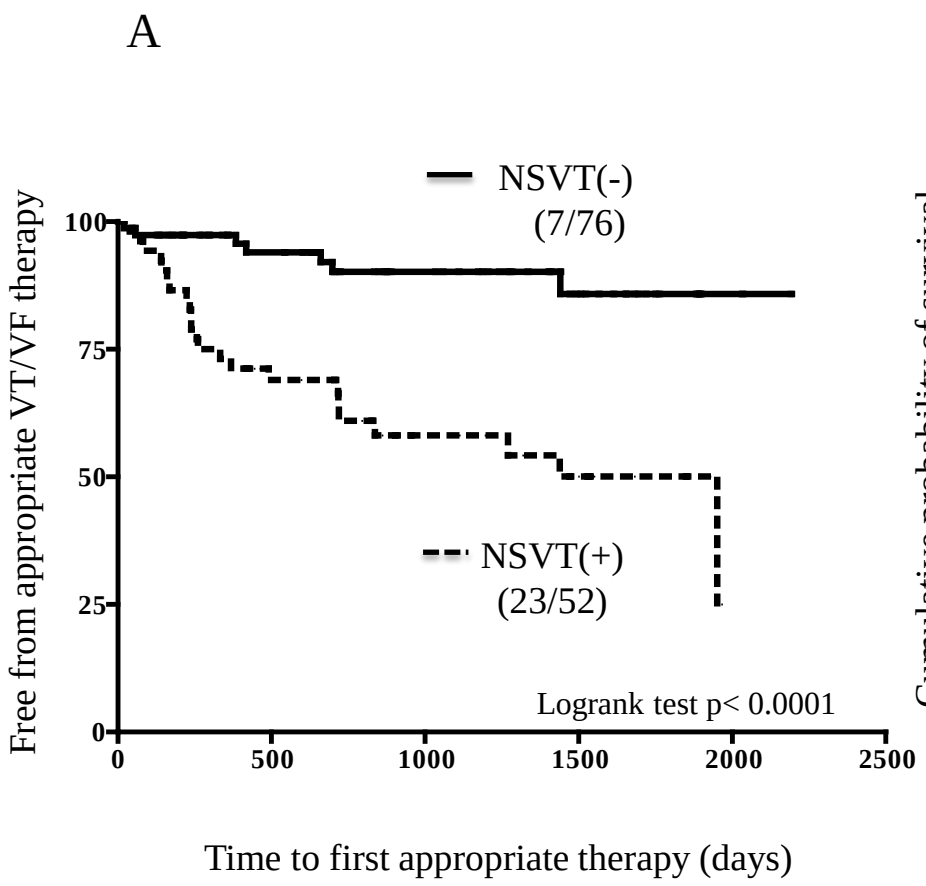
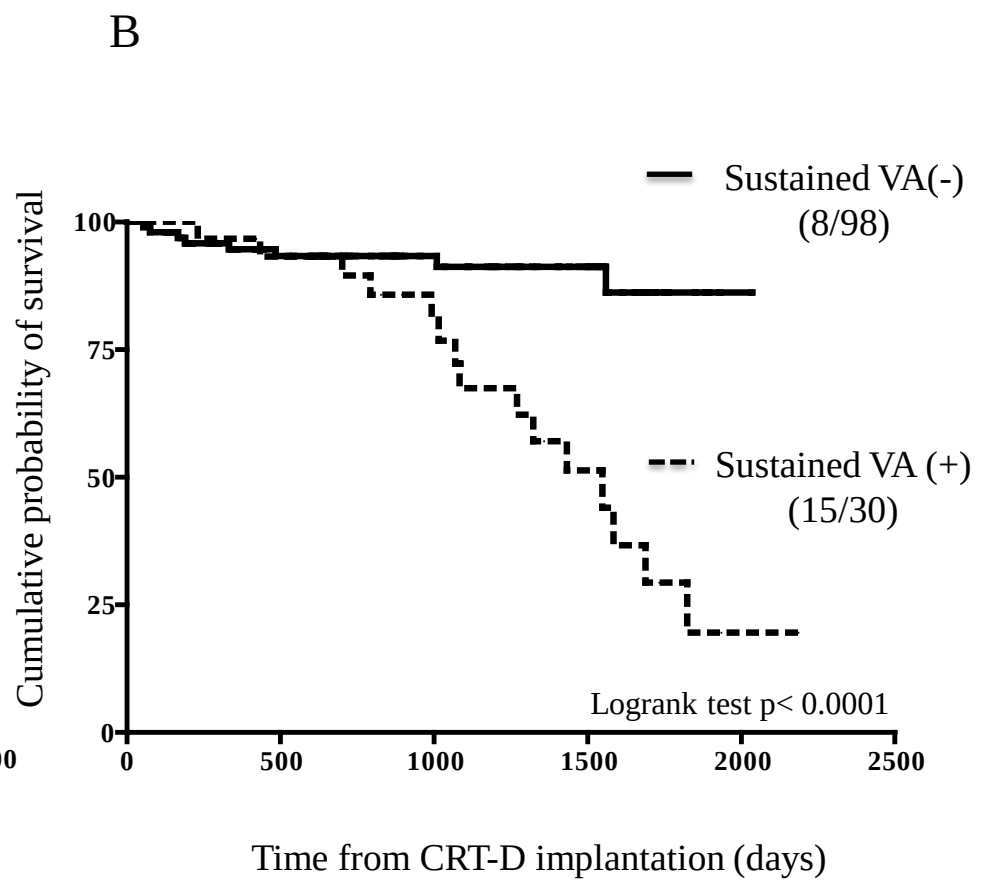


Figure 3


A
NSVT(-)
(7/76)
NSVT(+)
(23/52)
Logrank test p< 0.0001
Free from appropriate VT/VF therapy
100
75
50
25
0
0
500
1000
1500
2000
2500
Time to first appropriate therapy (days)


B
Sustained VA(-)
(8/98)
Sustained VA (+)
(15/30)
Logrank test p< 0.0001
Cumulative probability of survival
100
75
50
25
0
0
500
1000
1500
2000
2500
Time from CRT-D implantation (days)