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# Significant impact of electrical storm on mortality in patients with structural heart disease and an implantable cardiac defibrillator☆

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ABSTRACT

*Background:* Electrical storm (E-Storm), defined as multiple episodes of ventricular arrhythmias within a short period of time, is an important clinical problem in patients with an implantable cardiac defibrillator (ICD) including cardiac resynchronization therapy devices capable of defibrillation. The detailed clinical aspects of E-Storm in large populations especially for non-ischemic dilated cardiomyopathy (DCM), however, remain unclear.
*Objective:* This study was performed to elucidate the detailed clinical aspects of E-Storm, such as its predictors and prevalence among patients with structural heart disease including DCM.
*Methods:* We analyzed the data of the Nippon Storm Study, which was a prospective observational study involving 1570 patients enrolled from 48 ICD centers. For the purpose of this study, we evaluated 1274 patients with structural heart disease, including 482 (38%) patients with ischemic heart disease (IHD) and 342 (27%) patients with DCM.
*Results:* During a median follow-up of 28 months (interquartile range: 23 to 33 months), E-Storm occurred in 84 (6.6%) patients. The incidence of E-Storm was not significantly different between patients with IHD and patients with DCM (log-rank $p = 0.52$). Proportional hazard regression analyses showed that ICD implantation for secondary prevention of sudden cardiac death ($p = 0.0001$) and QRS width ($p = 0.015$) were the independent risk factors for E-storm. In a comparison between patients with and without E-Storm, survival curves after adjustment for clinical characteristics showed a significant difference in mortality.
*Conclusion:* E-Storm was associated with subsequent mortality in patients with structural heart disease including DCM.
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## 1. Introduction

Implantable cardiac defibrillators (ICDs) including cardiac resynchronization therapy devices capable of defibrillation (CRT-Ds), have become an established therapeutic option for reducing the risk of sudden cardiac death [1–5]. However, an ICD itself cannot prevent the occurrence of tachycardia attacks, and some patients may develop electrical storm (E-Storm) and receive shock deliveries or antitachycardia pacing (ATP) within a short period of time [6,7]. Patients who receive ICD shocks for termination of any arrhythmias have been shown to be associated with a substantially higher risk of death than patients who do not receive such shocks [8,9]. The incidence, predictive factors, and

*Abbreviations:* AF/AFL, atrial fibrillation and/or atrial flutter; ATP, antitachycardia pacing; CRT-D, cardiac resynchronization therapy device capable defibrillation; DCM, non-ischemic dilated cardiomyopathy; E-Storm, electrical storm; ICD, implantable cardiac defibrillator; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; VF, ventricular fibrillation; VT, ventricular tachycardia.

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clinical prognosis of patients with E-Storm were relatively well known in patients with ischemic heart disease (IHD) [10–13], but data are still lacking for other underlying heart diseases, especially in non-ischemic dilated cardiomyopathy (DCM).

The Nippon Storm Study was a prospective observational study designed to recruit clinical data from patients on ICD therapy [14,15] to investigate the incidence and the clinical characteristics of patients who develop E-Storm in Japan where DCM is relatively common compared to other Western countries.

## 2. Methods

### 2.1. Registration

The details of the overall study design of the Nippon Storm Study have been published [14,15]. Briefly, the Nippon Storm Study was organized by the Japanese Heart Rhythm Society and Japanese Society of Electrocardiology. Web site registration of patients was conducted in 48 Japanese ICD centers (Appendix A), and the Japanese Heart Rhythm Society collected data from physicians who input the patients' data. According to the guidelines for implantation of an ICD, indication and purpose of implantation was determined by attending cardiologists of each center.

### 2.2. ICD programing

The ICD was programmed at the physician's discretion. Some discrimination algorithms such as PR Logic and Wavelet (Medtronic, Minneapolis, MN), Rhythm ID (Boston Scientific, Marlborough, MA), and Morphology Discrimination plus AV Rate Branch (St. Jude Medical, St. Paul, MN) were used.

The ventricular fibrillation (VF) zone was >188 to 200 bpm with at least one train of ATP before the shock, and the ventricular tachycardia (VT) zone was >140 to 160 bpm with at least three trains of ATP before the shock, which were allowed to be modified according to patient's background.

Each E-Storm was managed by physicians according to their preference. If E-Storm was considered to be triggered by myocardial ischemia, heart failure, or electrolyte disorder, they were corrected immediately. If needed, an antiarrhythmic drug regimen comprising β-blockers, amiodarone, and lidocaine was administered sequentially or in combination. Some patients might undergo catheter ablation in the acute phase of E-Storm.

### 2.3. Follow-up

For the precise follow-up, we constructed a new tracking system called “Chaser” which was intended to minimize the loss of follow-up data. The data of interventions (both appropriate and inappropriate) from the ICD were sent at a maximum interval of 6 months, to the office of the Japanese Heart Rhythm Society through the Web site. The ICD interventions were classified into ATP, low-energy shocks, and high-energy shocks. E-Storm was defined as occurrence of at least three separate episodes of VT/VF within a 24-h period [6]. Every E-Storm was blindly adjudicated by two electro-physiologists (Drs. NA and KS) based on the intracardiac electrograms at the time of the event.

### 2.4. Data analysis

The patients' characteristics were analyzed from the baseline data which included age, sex, underlying heart disease, purpose of indication (primary or secondary), and complications related to implantation procedure.

As the main theme of this study, the incidence of E-Storm and its predictors were analyzed from the patients' baseline characteristics. Modalities of acute managements of E-Storm were analyzed. Finally, the prognosis was compared between the patients with and without E-Storm.

### 2.5. Statistics

Continuous baseline variables are presented as mean ± standard deviation, and categorical baseline variables are presented as n (%). When any two groups were compared, we applied the $\chi^2$ test for categorical variables and Student's *t*-test for continuous variables. For time-to-event outcomes, survival curves were created using the Kaplan–Meier method, and log rank tests were used for statistical hypothesis tests. The effects of covariates were explored with proportional hazard models using the hazard ratio (HR) and 95% confidential interval (95% CI). To compare subsequent mortality between patients with and without E-Storm, survival curves adjusted for covariates were created using the inverse probability weighting method [16]. Because the times to E-Storm differed among patients, we also performed a landmark analysis at the 6-, 12-, and 18-month landmark points. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). A $p$ value of $<0.05$ was considered statistically significant.

This study was conducted in accordance with the Helsinki Declaration and proved by Institutional Review Board of each institution. All patients gave written informed consent to participate in this study.

## 3. Results

### 3.1. Patients' baseline characteristics

In total, 1570 patients from 48 ICD centers in Japan (Appendix A) were enrolled. Of these, we focused on 1274 patients with structural heart disease including 482 (38%) patients with IHD and 342 (27%) patients with DCM.

The baseline characteristics of the 1274 patients are outlined in Table 1. At the time of implantation, the patients were 65 ± 12 years old, and 967 (76%) of the patients were male. With respect to the indications for ICD implantation, 638 (50%) and 636 (50%) patients received an ICD for primary and secondary prevention of sudden cardiac death, respectively. An ICD was implanted in 775 (61%) patients, and a CRT-D was implanted in 499 (39%) patients. The mean left ventricular ejection fraction (LVEF) was 38%. Of 1274 patients, IHD ($n = 482$) and DCM ($n = 342$) were major causes of structural heart diseases.

### 3.2. Incidence of E-Storm

During a median follow-up of 28 (range, 23–33) months, E-Storm occurred in 84 (6.6%) patients (annual event rate 2.8%). Regarding the underlying heart diseases, E-Storm occurred in 24 (5.0%) patients with IHD, 21 (6.1%) patients with DCM, 13 (6.4%) patients with hypertrophic cardiomyopathy, 7 (24%) patients with arrhythmogenic right ventricular cardiomyopathy, and 19 (8.7%) patients with other structural heart disease including valvular heart disease, cardiac sarcoidosis, or congenital heart disease, etc. (Fig. 1A). With respect to the reason for the ICD indication, E-Storm occurred in 4.2% of the patients with primary prevention and in 9.0% of the patients with secondary prevention. In a survival analysis, the E-Storm-free survival curves did not differ between IHD and DCM patients (log-rank $p = 0.52$).

**Table 1**
Baseline characteristics of patients with ICD/CRT-D with structural heart disease ($n = 1274$).

| Clinical characteristics | |
|---|---|
| Gender, man (%) | 967 (76%) |
| Age years | 65 ± 12 |
| *Underlying anatomic diagnosis* | |
| IHD | 482 (38%) |
| DCM | 342 (27%) |
| HCM | 204 (16%) |
| ARVC | 29 (2%) |
| Other | 218 (17%) |
| Primary prevention | 638 (50%) |
| Secondary prevention | 636 (50%) |
| ICD (%) | 775 (61%) |
| CRT-D (%) | 499 (39%) |
| NYHA I (%) | 375 (29%) |
| NYHA II (%) | 482 (38%) |
| NYHA III (%) | 365 (29%) |
| NYHA IV (%) | 52 (4%) |
| LVEF % | 38 ± 17 |
| *Medication* | |
| Beta-blocker (%) | 887 (70%) |
| Amiodarone (%) | 513 (40%) |
| ACEI or ARB | 750 (59%) |

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ARVC = arrhythmogenic right ventricular cardiomyopathy; CRT-D = cardiac resynchronization therapy device with defibrillator; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; ICD = implantable cardiac defibrillator; ICSD = implantable cardiac shock device; IHD = ischemic heart disease; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

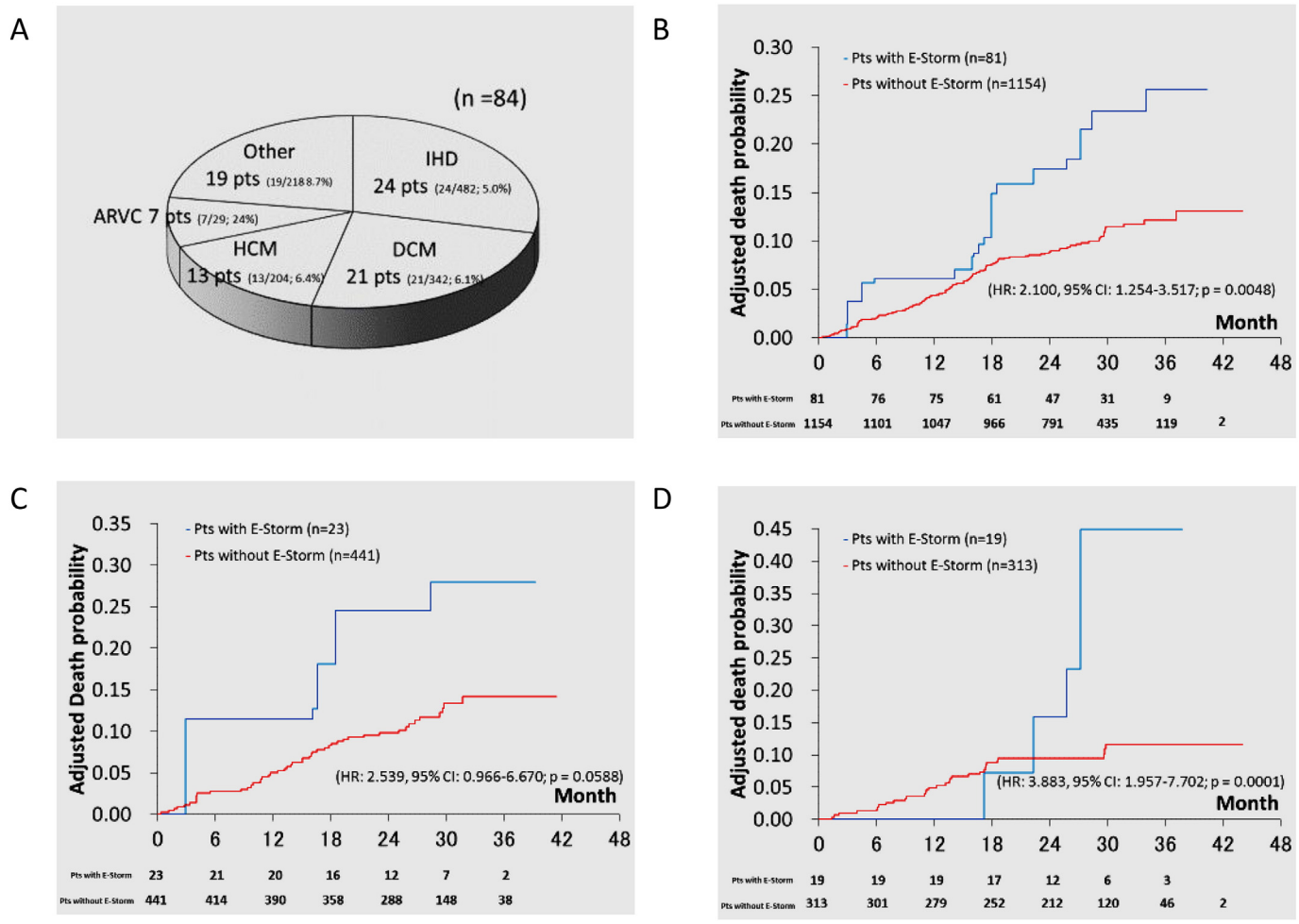



**Fig. 1.** (A) Incidence of electrical storm for each etiological underlying anatomic diagnosis. ARVC: arrhythmogenic right ventricular cardiomyopathy, DCM: dilated cardiomyopathy, HCM: hypertrophic cardiomyopathy, IHD: ischemic heart disease. (B) Kaplan–Meier curves adjusted for baseline characteristics using the inverse probability weighting method. There was a significant difference in the prognosis between patients with and without electrical storm (hazard ratio, 2.100; 95% confidence interval, 1.254–3.517; $p = 0.0048$). (C) Kaplan–Meier curves adjusted for baseline characteristics using the inverse probability weighting method only in patients with ischemic heart disease. There was a marginal difference in the prognosis between patients with and without electrical storm (hazard ratio, 2.539; 95% confidence interval, 0.966–6.670; $p = 0.0588$). (D) Kaplan–Meier curves adjusted for baseline characteristics using the inverse probability weighting method only in patients with non-ischemic dilated cardiomyopathy. There was a significant difference in the prognosis between patients with and without electrical storm (hazard ratio, 3.833; 95% confidence interval, 1.957–7.702; $p = 0.0001$).

### 3.3. Risks for E-Storm

Regarding the baseline characteristics between the patients with E-Storm and those without E-Storm, there was no significant difference in sex, age, type of shock device, symptoms of heart failure, LVEF, baseline heart rate, prevalence of atrial fibrillation and/or atrial flutter (AF/AFL), QT intervals, or medication. However, significantly more patients with than without E-Storm received an ICD for secondary prevention (68% vs. 49%, respectively; $p = 0.007$), and the QRS width was significantly greater in patients with than without E-Storm (141 ± 40 vs. 131 ± 35 ms, respectively; $p = 0.036$).

Both univariable and multivariate proportional hazard regression analyses of E-Storm showed that ICD implantation for secondary versus primary prevention of sudden cardiac death yielded a hazard ratio (HR) of 2.698 (95% CI, 1.634–4.456; $p = 0.0001$), and the QRS width (per 1 ms) was another risk of developing E-storm with an HR, 1.008 (95% CI, 1.001–1.014; $p = 0.015$): the hazard risk increases by 8% for each 10-ms inclement of the QRS width (Table 2).

### 3.4. Acute management of E-Storm

Acute managements of E-Storm were performed in 59 patients by adjustment or increase in the number of and/or doses of antiarrhythmic drugs in 31 patients (administration of intravenous amiodarone in 14, and intravenous nifekalant in 8 patients).

A total of 17 patients with E-Storm underwent catheter ablation in the acute phase of E-Storm, and multivariate analysis showed that catheter ablation was not associated with a significant decrease of death in E-Storm patients (HR, 0.885; 95% CI, 0.470–1.665; $p = 0.704$).

### 3.5. E-Storm and prognosis

Since there were significant differences in the baseline clinical characteristics between patients with and without E-Storm, we also evaluated the Kaplan–Meier curves adjusted for the baseline characteristics using the inverse probability weighting method [16]. We included all variables in Table 2 as the adjusted covariates. The adjusted Kaplan–Meier curves showed a significant difference in mortality between patients with and without E-Storm (log-rank $p = 0.005$) (Fig. 1B). The median duration between E-Storm and death was 12 months, and 5 out of 17 patients died within 3 months. Among only patients with IHD or DCM, the adjusted Kaplan–Meier curves regarding mortality showed a marginal difference in IHD (log-rank $p = 0.0588$) (Fig. 1C) and a significant difference in DCM (log-rank $p = 0.0001$) (Fig. 1D) between patients with and without E-Storm.

**Table 2**
Hazard ratios for E-Storm on clinical variables.

| | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *P* value | HR | 95% CI | *P* value |
| *Clinical characteristics* | | | | | | |
| Gender, man | 1.11 | 0.666–1.85 | 0.69 | | | |
| Age years | 1.018 | 0.999–1.038 | 0.065 | | | |
| Primary prevention | 2.195 | 1.388–3.470 | 0.0008 | 2.698 | 1.634–4.456 | 0.0001 |
| Secondary prevention | | | | | | |
| ICD CRT-D | 1.075 | 0.696–1.663 | 0.74 | | | |
| NYHA II (vs NYHA I) | 0.977 | 0.569–1.679 | 0.93 | | | |
| NYHA III (vs NYHA I) | 1.389 | 0.812–2.376 | 0.23 | | | |
| NYHA IV (vs NYHA I) | 0.336 | 0.045–2.486 | 0.29 | | | |
| Cr mg/dl | 0.948 | 0.792–1.136 | 0.56 | | | |
| Hb g/dl | 1.002 | 0.898–1.116 | 0.98 | | | |
| LVEF % | 0.989 | 0.976–1.002 | 0.11 | | | |
| *Baseline ECG* | | | | | | |
| Heart rate/min | 0.991 | 0.975–1.007 | 0.25 | | | |
| Baseline rhythm of AF/AFL | 1.331 | 0.730–2.427 | 0.35 | | | |
| QRS-width ms | 1.007 | 1.001–1.013 | 0.015 | 1.008 | 1.001–1.014 | 0.015 |
| QT-duration ms | 1.001 | 0.998–1.005 | 0.48 | | | |
| *Medication* | | | | | | |
| Beta-blocker (%) | 1.03 | 0.64–1.64 | 0.90 | | | |
| Amiodarone (%) | 1.47 | 0.96–2.25 | 0.078 | | | |
| ACEI or ARB | 0.6 | 0.44–1.08 | 0.10 | | | |

ACEI = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; AFL = atrial flutter; ARB = angiotensin II receptor blocker; CI = confidence interval; Cr = creatinine; CRT-D = cardiac resynchronization therapy device with defibrillator; E-Storm = electrical storm; Hb = hemoglobin; HR = hazard ratio; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

We further evaluated the adjusted Kaplan–Meier curves using the landmark analysis because the times to E-Storm differed among patients. The landmark analysis was performed at the 6-, 12-, and 18-month landmark points. The respective results are summarized in Fig. 2A to 2C; the results also showed significant or marginal differences in the curves regarding prognosis between patients with and without E-Storm.

## 4. Discussion

The three main findings of this study are as follows. First, E-Storm occurred in 6.6% of the patients with structural heart disease during a median follow-up of 28 months (annual event rate 2.8%), and the incidence was similar between IHD and DCM patients. Second, multivariate analysis revealed that secondary prevention of sudden cardiac death as the indication for ICD implantation and the QRS width were independent predictors of E-Storm. Third, the survival curves adjusted for covariates revealed a significant difference in mortality between the patients with and without E-Storm, even in patients with DCM.

### 4.1. Incidence of E-Storm

In the present study, the annual event rate of E-Storm was 2.8% in the patients with structural heart disease (IHD patients for primary prevention: 1.2%, IHD patients for secondary prevention: 2.7%, DCM patients for primary prevention: 2.1%, and DCM patients for secondary prevention: 3.8%). Generally, the incidence of E-Storm is expected to be lower in the patients who have an ICD for primary prevention than in those for secondary prevention. The Nippon Storm Study is the first study to clearly demonstrate that ICD patients for secondary prevention are exposed to have twice the risk of E-Storm as compared to those for primary prevention. The previous clinical studies including ICD patients for secondary prevention reported a higher annual incidence of E-Storm (7 to 11%) than our results [6,17,18]. The relatively low incidence of E-Storm in the present study can be explained by the recent trend to program higher rate cutoffs and longer arrhythmia-detection windows for VT/VF detection which may lead to a reduction of unnecessary interventions from ICDs. Furthermore, to the best of our knowledge, only limited data exist regarding E-Storm in ICD patients with DCM for primary prevention. In this study, we could clearly demonstrate that the annual rate of E-Storm in 241 DCM patients for primary prevention was 2.1%. We also found no significant difference in the cumulative probability of E-Storm between patients with IHD and patients with DCM (24/482 vs. 21/342, respectively; log-rank $p = 0.52$).

### 4.2. Predictors of E-Storm

Several reports have shown that significant predictors of E-Storm are previous VT/VF episodes, a reduced LVEF, chronic renal failure, and advanced age [7,19–21]. In the present study, secondary prevention of sudden cardiac death as the indication for ICD implantation was an independent predictor of E-Storm; this finding is comparable with those in previous reports [7,19]. Our results are comprehensive considering the difference in the incidence of appropriate ICD therapy between patients who have ICD for secondary versus primary prevention of sudden cardiac death because patients who have already experienced an arrhythmic episode are more prone to develop further ventricular arrhythmias after ICD implantation. In contrast, although the LVEF tended to be lower in patients with E-Storm, neither the LVEF nor advanced age had predictive power for the occurrence of ES. This is consistent with the findings reported by Hohnloser et al. [12] and may have been due to the patients' baseline characteristics, including an etiology of underlying heart disease with a relatively well-preserved LVEF (e.g., arrhythmogenic right ventricular cardiomyopathy or hypertrophic cardiomyopathy).

Arya et al. [22] reported that a QRS width of ≥120 ms increased the risk of E-Storm. Other investigators have also reported a relationship between a prolonged QRS interval and VT/VF events in patients with ICD [23]. The QRS width may indicate the extent of myocardial fibrosis, which could result in a development of an arrhythmic substrate, especially depolarization abnormalities, leading to VT/VF.

### 4.3. E-Storm and prognosis

Previous data have shown that patients with E-Storm have an increased risk of cardiac death during follow-up. In the AVID study [6], patients with E-Storm displayed a 2-fold higher risk of all-cause mortality. Sesselberg et al. [7] reported that E-Storm was the most important independent predictor of mid-term cardiac death, with 7-fold increased risk (particularly significant in the first 3 months after E-storm) in the MADIT II trial. In addition, Poole et al. [8] reported that multiple shocks were associated with an 8-fold higher risk of death in a subanalysis of the SCD-HeFT trial. Moreover, a recent meta-analysis of a large population among 13 studies also revealed that E-Storm was strongly associated with a high mortality rate [24]. Based on the fact that all previous studies demonstrated a significantly poor prognosis in patients with E-Storm [6–8,24], it can be supposed that a direct comparison method was used without accounting for different patient backgrounds. Because of the many differences in clinical characteristics between the two groups, particularly in the QRS width and the proportion of patients with secondary prevention of sudden cardiac death as the indication for ICD implantation, we evaluated the Kaplan–Meier curves after adjustment for covariates. The results also revealed a significant difference in mortality between patients with and without E-Storm. To the best of our knowledge, this is the first report to assess the relationship between E-Storm and prognosis after adjustment for clinical characteristics, which is a novel aspect of our study. Our results could show that the adjusted Kaplan–Meier curves regarding mortality showed a significant difference between patients with and without E-Storm among only patients with DCM since our cohort included a high number of patients with non-ischemic cardiomyopathy.

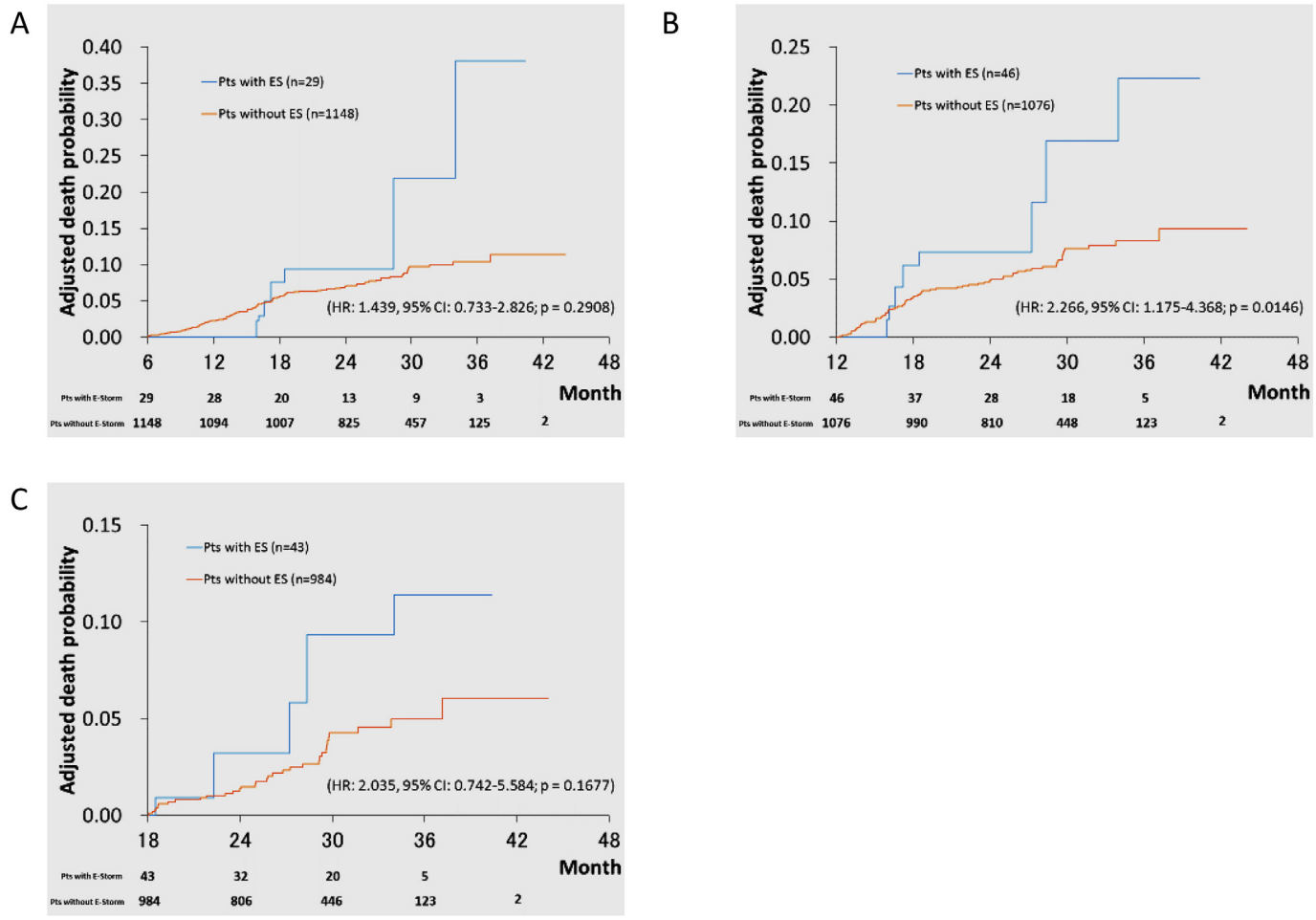



**Fig. 2.** (A) Cumulative probability of death in patients with and without electrical storm using landmark analysis at the 6-month landmark point. (B) Cumulative probability of death in patients with and without electrical storm using landmark analysis at the 12-month landmark point. (C) Cumulative probability of death in patients with and without electrical storm using landmark analysis at the 18-month landmark point.

Little was known regarding the mechanisms of an increase in mortality associated with E-Storm. Sub-analyses of the AVID study and the MADIT-II trial indicated a high risk for early death within 3 months in patients who experienced E-Storm [6,7]. In our study, the median duration between E-Storm and death was 12 months, however, 5 out of 17 (29%) patients died within 3 months after E-Storm, which was identical to the previous reports. Moreover, compared to patients with isolated VT/VF as well as those without events, patients with E-Storm showed significantly higher mortality during the follow-up similar to the sub-analyses of the AVID study and the MADIT-II trial. Thus our data also provides additional support to the notion that E-Storm contributes to the observed excess mortality.

Guerra et al. reported that E-Storm could be considered as a clinical manifestation of HF worsening [25]. Among the 84 patients with E-Storm in this study, worsening of heart failure was seen in 28 patients at the first event of E-Storm. Moreover, 16 patients had HF hospitalization at the median duration of 6.5 (2.6–10.5) months after the occurrence of E-Storm, which may explain the mechanisms of an increase in mortality associated with E-Storm.

### 4.4. Limitations

This study had several limitations. First, its prospective observational design and multicenter registry resulted in a lack of randomization and thus potentially hidden bias. Although caution should be used when applying our results to other geographic settings, especially patients in Western countries, our cohort reflects the real-world clinical setting of Asian patients with ICD, especially those with non-ischemic cardiomyopathy. Because few large studies of E-Storm have evaluated patients with non-ischemic cardiomyopathy, we believe that the present data offer novel insights regarding E-Storm in ICD therapy.

Second, a relatively low heart rate programming for VT/VF detection in our series may increase the incidence of E-Storm by providing unnecessary therapies from ICD for self-terminating VT/VF. However, this programming trend was observed mainly in secondary prevention patients, and a detection interval was determined based on the lowest rate of clinical VT in each patient. In primary prevention patients, a higher detection rate and longer duration interval were used compared with secondary prevention patients.

Third, is with respect to clinical management which is usually done in the combination with antiarrhythmic medications, sympathetic blockade, hemodynamic support, anesthesia and/or catheter ablation [26]. In this study, we could not find the influence of adjustment or increase of the number of and/or doses of antiarrhythmic drugs on the subsequent mortality or the heart failure hospitalization since beta-blockers and amiodarone were prescribed in 70% and 40% of the study subjects at baseline, respectively. Regarding the role of catheter ablation, several reports have shown the effectiveness of catheter ablation for management of E-Storm in terms of prognosis [27,28]. On the other hand, recent clinical trial of VANISH study [29] showed the fact that death probability is comparable between patients undergoing catheter ablation and those receiving antiarrhythmic drug medication, suggesting that catheter ablation provides less prognostic benefits than expected. The small number of patients in the present study ($n = 17$)

who underwent catheter ablation in the acute phase of E-Storm may have affected the result that catheter ablation was not independently associated with a decreased risk of death in patients with E-Storm. Further studies of this issue in larger populations, especially regarding patients with DCM, are needed.

## 5. Conclusion

In the clinical setting, E-Storm is not rare in patients with DCM or IHD. E-Storm episodes require proper emergency-based management, and are significantly associated with subsequent mortality.

## Conflict of interest

No financial support was received for this study from any specific company except the Japan Arrhythmia Device Industry Association. The authors declare no other relationships with industry and no specific unapproved use of any compound or product.

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## Appendix A. The 48 participating Japanese implantable cardiac shock device centers in the present study

Hokko Memorial Hospital
Second Department of Internal Medicine, Sapporo Medical University Hospital
Department of Cardiovascular Medicine, Hokkaido University Hospital
Department of Cardiovascular Medicine, Hirosaki University Graduate School
Department of Cardiovascular Medicine, Tohoku University Hospital
Cardiovascular Division, Faculty of Medicine, University of Tsukuba
Department of Internal Medicine, Jichi Medical University
Division of Cardiology, Gunma Prefectural Cardiovascular Center
Cardiovascular Medicine, Saitama Medical University International Medical Center
Department of Cardiology, Juntendo University Urayasu Hospital
Department of Cardiovascular Medicine, Chiba University Hospital
Division of Cardiology, Sakakibara Heart Institute
First Department of Medicine, Nippon Medical School Hospital
Department of Cardiology, Keio University School of Medicine
Department of Cardiovascular Medicine, Tokyo Metropolitan Hiroo Hospital
Division of Cardiology, Department of Medicine, Showa University
Department of Cardiology, Jikei University School of Medicine
Department of Cardio-angiology, Kitasato University
Department of Heart Rhythm Management, Yokohama Rosai Hospital
Yokohama City University School of Medicine, Department of Medical Science and Cardiorenal Medicine
Showa University Fujigaoka Hospital
Department of Cardiology, Yokohama Minami Kyousai Hospital
Department of Cardiovascular Biology and Medicine, Niigata University Graduate School of Medical and Dental Sciences
Division of Cardiology, Tachikawa General Hospital
Department of Cardiovascular Medicine, Shinshu University School of Medicine, Graduate School of Medicine
Department of Cardiology, Nagoya University
Cardiovascular Medicine, Toyohashi Heart Center
Japanese Red Cross Nagoya Daini Hospital
Department of Cardiology, Fujita Health University School of Medicine
Cardiovascular Medicine, Kyoto University Hospital
Department of Cardiovascular Medicine, Kyoto Prefectural University School of Medicine
Cardiovascular Center, Sakurabashi Watanabe Hospital
Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center
Division of Cardiology, Department of Medicine, Faculty of Medicine, Kinki University
Department of Cardiovascular Medicine, Osaka City University Hospital
Department of Cardiology, Osaka General Medical Center
Department of Cardiology, Hyogo Brain And Heart Center
Department of Cardiology, Kobe University Hospital
Department of Cardiovascular Medicine, Okayama University
Department of Cardiovascular Surgery, Hiroshima University Graduate School of Medicine
Division of Cardiology, Department of Internal Medicine II, Yamaguchi University Hospital
Department of Cardiology, Ehime University Graduate School of Medicine
Department of Cardiovascular Medicine, Kokura Memorial Hospital
Department of Cardiology, Fukuoka University School of Medicine
Department of Heart Rhythm Management, University of Occupational and Environmental Health
Department of Cardiology, Saiseikai Kumamoto Hospital
Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University
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## References

[1] The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators, A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias, N. Engl. J. Med. 337 (1997) 1576–1583.
[2] A.J. Moss, W. Zareba, W.J. Hall, H. Klein, D.J. Wilber, D.S. Cannom, J.P. Daubert, S.L. Higgins, M.W. Brown, M.L. Andrews, Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction, N. Engl. J. Med. 346 (2002) 877–883.
[3] G.H. Bardy, K.L. Lee, D.B. Mark, J.E. Poole, D.L. Packer, R. Boineau, M. Domanski, C. Troutman, J. Anderson, G. Johnson, S.E. McNulty, N. Clapp-Channing, L.D. Davidson-Ray, E.S. Fraulo, D.P. Fishbein, R.M. Luceri, J.H. Ip, Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure, N. Engl. J. Med. 352 (2005) 225–237.
[4] M.R. Bristow, L.A. Saxon, J. Boehmer, S. Krueger, D.A. Kass, T. De Marco, P. Carson, L. DiCarlo, D. DeMets, B.G. White, D.W. DeVries, A.M. Feldman, Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure, N. Engl. J. Med. 350 (2004) 2140–2150.
[5] A.J. Moss, W.J. Hall, D.S. Cannom, H. Klein, M.W. Brown, J.P. Daubert, N.A. Estes 3rd, E. Foster, H. Greenberg, S.L. Higgins, M.A. Pfeffer, S.D. Solomon, D. Wilber, W. Zareba, Cardiac-resynchronization therapy for the prevention of heart-failure events, N. Engl. J. Med. 361 (2009) 1329–1338.
[6] D.V. Exner, S.L. Pinski, D.G. Wyse, E.G. Renfroe, D. Follmann, M. Gold, K.J. Beckman, J. Coromilas, S. Lancaster, A.P. Hallstrom, Electrical storm presages nonsudden death: the antiarrhythmics versus implantable defibrillators (AVID) trial, Circulation 103 (2001) 2066–2071.
[7] H.W. Sesselberg, A.J. Moss, S. McNitt, W. Zareba, J.P. Daubert, M.L. Andrews, W.J. Hall, B. McClinitic, D.T. Huang, Ventricular arrhythmia storms in postinfarction patients with implantable defibrillators for primary prevention indications: a MADIT-II substudy, Heart Rhythm. 4 (2007) 1395–1402.
[8] J.E. Poole, G.W. Johnson, A.S. Hellkamp, J. Anderson, D.J. Callans, M.H. Raitt, R.K. Reddy, F.E. Marchlinski, R. Yee, T. Guarnieri, M. Talajic, D.J. Wilber, D.P. Fishbein, D.L. Packer, D.B. Mark, K.L. Lee, G.H. Bardy, Prognostic importance of defibrillator shocks in patients with heart failure, N. Engl. J. Med. 359 (2008) 1009–1017.
[9] M.O. Sweeney, L. Sherfesee, P.J. DeGroot, M.S. Wathen, B.L. Wilkoff, Differences in effects of electrical therapy type for ventricular arrhythmias on mortality in implantable cardioverter-defibrillator patients, Heart Rhythm. 7 (2010) 353–360.
[10] M.A. Wood, P.M. Simpson, B.S. Stambler, J.M. Herre, R.C. Bernstein, K.A. Ellenbogen, Long term temporal patterns of ventricular tachyarrhythmias, Circulation 91 (1995) 2371–2377.
[11] S.C. Credner, T. Klingenheben, O. Mauss, C. Sticherling, S.H. Hohnloser, Electrical storm in patients with transvenous implantable cardioverter-defibrillators: incidence, management and prognostic implications, J. Am. Coll. Cardiol. 32 (1998) 1909–1915.
[12] S.H. Hohnloser, H.R. Al-Khalidi, C.M. Pratt, J.M. Brum, D.S. Tatla, P. Tchou, P. Dorian, Electrical storm in patients with an implantable defibrillator: incidence, features, and preventive therapy: insights from a randomized trial, Eur. Heart J. 27 (2006) 3027–3032.
[13] M. Gasparini, M. Lunati, M. Landolina, M. Santini, L. Padeletti, G. Perego, A. Vincenti, A. Curnis, A. Carboni, A. Denaro, A. Spotti, A. Grammatico, F. Regoli, G. Boriani, Electrical storm in patients with biventricular implantable cardioverter defibrillator: incidence, predictors and prognostic implications, Am. Heart J. 156 (2008) 847–854.
[14] T. Kurita, T. Noda, T. Nitta, H. Furushima, A. Shimizu, T. Ohe, Y. Aizawa, Y. Chiba, Nippon Storm Study design, J. Arrhythmia 28 (2012) 277–279.
[15] T. Noda, T. Kurita, T. Nitta, H. Abe, S. Watanabe, H. Furushima, N. Matsumoto, T. Toyoshima, A. Shimizu, H. Mitamura, T. Ohe, Y. Aizawa, Appropriate duration of driving restrictions after inappropriate therapy from implantable cardiac shock devices-interim analysis of the Nippon Storm Study, Circ. J. 78 (2014) 1989–1991.
[16] S.R. Cole, M.A. Hernán, Adjusted survival curves with inverse probability weights, Comput. Methods Prog. Biomed. 75 (2004) 45–49.
[17] D. Bänsch, D. Böcker, J. Brunn, M. Weber, G. Breithardt, M. Block, Clusters of ventricular tachycardias signify impaired survival in patients with idiopathic dilated

cardiomyopathy and implantable cardioverter defibrillators, J. Am. Coll. Cardiol. 36 (2000) 566–573.
[18] M. Takigawa, T. Noda, T. Kurita, N. Aihara, Y. Yamada, H. Okamura, K. Satomi, K. Suyama, W. Shimizu, S. Kamakura, Predictors of electrical storm in patients with idiopathic dilated cardiomyopathy—how to stratify the risk of electrical storm, Circ. J. 74 (2010) 1822–1829.
[19] K.A. Gatzoulis, G.K. Andrikopoulos, T. Apostolopoulos, E. Sotiropoulos, G. Zervopoulos, J. Antoniou, S. Brili, C.I. Stefanadis, Electrical storm is an independent predictor of adverse long-term outcome in the era of implantable defibrillator therapy, Europace 7 (2005) 184–192.
[20] F. Brigadeau, C. Kouakam, D. Klug, C. Marquié, A. Duhamel, F. Mizon-Gérard, D. Lacroix, S. Kacet, Clinical predictors and prognostic significance of electrical storm in patients with implantable cardioverter defibrillators, Eur. Heart J. 27 (2006) 700–707.
[21] F. Streitner, J. Kuschyk, C. Veltmann, E. Mahl, C. Dietrich, R. Schimpf, C. Doesch, I. Streitner, C. Wolpert, M. Borggrefe, Predictors of electrical storm recurrences in patients with implantable cardioverter-defibrillators, Europace 13 (2011) 668–674.
[22] A. Arya, M. Haghjoo, M.R. Dehghani, A.F. Fazelifar, M.H. Nikoo, A. Bagherzadeh, M.A. Sadr-Ameli, Prevalence and predictors of electrical storm in patients with implantable cardioverter-defibrillator, Am. J. Cardiol. 97 (2006) 389–392.
[23] R. Dhar, A.A. Alsheikh-Ali, N.A. Estes 3rd, A.J. Moss, W. Zareba, J.P. Daubert, H. Greenberg, R.B. Case, D.M. Kent, Association of prolonged QRS duration with ventricular tachyarrhythmias and sudden cardiac death in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II), Heart Rhythm. 5 (2008) 807–813.
[24] F. Guerra, M. Shkoza, L. Scappini, M. Flori, A. Capucci, Role of electrical storm as a mortality and morbidity risk factor and its clinical predictors: a meta-analysis, Europace 16 (2014) 347–353.
[25] F. Guerra, M. Flori, P. Bonelli, F. Patani, A. Capucci, Electrical storm and heart failure worsening in implantable cardiac defibrillator patients, Europace 17 (2015) 247–254.
[26] L. Rivard, J. Andrade, Innovative approaches to arrhythmic storm: the growing role of interventional procedures, Can. J. Cardiol. 33 (2017) 44–50.
[27] C. Carbucicchio, M. Santamaria, N. Trevisi, G. Maccabelli, F. Giraldi, G. Fassini, S. Riva, M. Moltrasio, M. Cireddu, F. Veglia, P. Della Bella, Catheter ablation for the treatment of electrical storm in patients with implantable cardioverter-defibrillators: short and long-term outcomes in a prospective single-center study, Circulation 117 (2008) 462–469.
[28] A. Arya, K. Bode, C. Piorkowski, A. Bollmann, P. Sommer, T. Gaspar, U. Wetzel, D. Husser, H. Kottkamp, G. Hindricks, Catheter ablation of electrical storm due to monomorphic ventricular tachycardia in patients with nonischemic cardiomyopathy: acute results and its effect on long-term survival, Pacing Clin. Electrophysiol. 33 (2010) 1504–1509.
[29] J.L. Sapp, G.A. Wells, R. Parkash, W.G. Stevenson, L. Blier, J.F. Sarrazin, B. Thibault, L. Rivard, L. Gula, P. Leong-Sit, V. Essebag, P.B. Nery, S.K. Tung, J.M. Raymond, L.D. Sterns, G.D. Veenhuyzen, J.S. Healey, D. Redfearn, J.F. Roux, A.S. Tang, Ventricular tachycardia ablation versus escalation of antiarrhythmic drugs, N. Engl. J. Med. 375 (2016) 111–121.