博士学位論文

植え込み型除細動器留置患者の心房細動が予後に与える影響に関して
ーニッポンストームのサブ解析ー

丸山　将広

Doctoral Dissertation

Impact of atrial fibrillation/flutter on outcomes of patients with implantable cardioverter defibrillators: A sub-analysis of the Nippon Storm study

August 2021

Masahiro Maruyama

論博

同　意　書

2021　年　8月　12日

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Original article

Impact of atrial fibrillation/flutter on outcomes of patients with implantable cardioverter defibrillators: A sub-analysis of the Nippon Storm study

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ABSTRACT

Background: Implantable cardioverter-defibrillator and cardiac resynchronization therapy using a defibrillator (ICD/CRT-D) are established means of reducing mortality due to ventricular arrhythmia. Although atrial fibrillation/flutter (AF) is the most common cardiac arrhythmia in patients with heart disease, the impact of AF on the prognosis of patients with ICD/CRT-D remains controversial.

Methods and Results: We analyzed data from the Nippon Storm Study, a prospective observational study of 1570 patients that was conducted at 48 Japanese ICD centers. We allocated 1549 participants to AF and non-AF groups, compared their clinical data at the time of enrollment, and monitored the incidences of mortality, hospitalization, and appropriate and inappropriate ICD/CRT-D therapy during a median 28 months. When the AF (n = 257, 16.6%) and non-AF-(n = 1292, 83.4%) groups were compared, the AF group was older (67.7 *vs.* 61.4 years; $p<0.0001$), and had lower left ventricular ejection fraction (38.0 ± 17.0% vs. 43.5 ± 18.9%; $p<0.0001$). During follow up, mortality was significantly higher in the AF than the non-AF group ($p<0.0001$). In multivariate analysis, AF was significantly associated with all-cause mortality [p = 0.013; hazard ratio (HR)=1.62]. Inappropriate ICD/CRT-D therapy occurred in 40/257 patients (15.6%) and AF was associated with a higher prevalence of inappropriate ICD/CRT-D therapy ($p<0.0001$; HR=2.25).

Conclusion: The presence of AF at ICD/CRT-D implantation carries subsequent independent risks of 1.62-fold for death and 2.25-fold for inappropriate therapy.

Introduction

In general, the prevalence of atrial fibrillation/flutter (AF) increases with the severity of chronic heart failure and is associated with further deterioration and higher mortality in patients with heart failure (HF). Implantable cardiac shock devices, such as the implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy with a defibrillator (CRT-D), are established means of reducing mortality due to ventricular arrhythmia in patients with HF. However, AF, which is thought to be present in up to 20% of ICD patients [1], limits the clinical usefulness of ICD, because it can provoke inappropriate shock therapies and cause a deterioration in patient quality of life (QOL).

The impact of AF on the prognosis of patients with ICD is controversial [2,3] and it remains unclear how AF influences the incidences of hospitalization due to HF, ventricular tachyarrhythmia, mortality due to arrhythmia, inappropriate ICD therapy, and hemorrhage. Therefore, the aim of the present study was to provide further information regarding the importance of AF in Japanese pa-

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tients with ICD or CRT-D by the analysis of data from a cohort study (the Nippon Storm study) [4].

Methods

Participants and study protocol

We analyzed data from the Nippon Storm Study, which was a multi-center, prospective, observational study of 1570 patients in Japan who were being newly treated using ICD or CRT-D. This study demonstrated that the incidence of electrical storm (ES) was 6.6% (84 of 1570 patients) during a median follow-up period of 28 months. The details of the overall study design have been published previously [5]. Briefly, the study was organized by the Japanese Heart Rhythm Society and the Japanese Society of Electrocardiology. Website registration of patients was conducted in 48 Japanese ICD centers and the Japanese Heart Rhythm Society collected data regarding the participants that were entered by their physicians. According to the guidelines for implantation of an ICD, the indication and purpose of implantation was determined by the attending cardiologist at each center.

ICD/CRT-D programming

Each ICD or CRT-D was programmed at the physician's discretion. Various discrimination algorithms, such as PR Logic and Wavelet (Medtronic, Minneapolis, MN, USA), Rhythm ID (Boston Scientific, Marlborough, MA, USA), and Morphology Discrimination plus AV Rate Branch (St. Jude Medical, St. Paul, MN, USA), were used. The ventricular fibrillation (VF) zone was defined as >188 to 200 bpm, with at least one train of anti-tachycardia pacing (ATP) before the ICD-delivered shock; and the ventricular tachycardia (VT) zone was defined as >140 to 160 bpm, with at least three trains of ATP before the ICD-delivered shock; although modifications were permitted on the basis of each patient's background.

Follow up

For comprehensive follow up, we constructed a new tracking system called "Chaser" that was intended to minimize the loss of follow-up data. Data regarding both appropriate and inappropriate interventions that were obtained from the ICD were sent at maximum intervals of 6 months to the office of the Japanese Heart Rhythm Society *via* the dedicated study website.

Data analysis

Twenty-one patients were lost to follow up. We allocated the remaining 1549 participants to an AF group and a non-AF group, according to whether they had AF or not at the time of enrollment.

The following baseline patient characteristics were assessed: age, sex, underlying heart disease [for example, ischemic heart disease (IHD), non-ischemic dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), or Brugada syndrome], left ventricular ejection fraction (LVEF), indication for ICD (primary or secondary), and renal function (estimated glomerular filtration rate, eGFR). The primary outcomes were the incidences of death, HF-related hospitalization, inappropriate ICD therapy, and ICD shock. An inappropriate event was defined as the delivery of any inappropriate ICD or CRT-D therapy, including ATP or shock for sinus tachycardia, AF, regular supraventricular tachycardia, or for non-arrhythmic events (such as detected noise, myopotentials, electromagnetic interference, or T-wave over-sensing). Arrhythmic death was defined as the documentation of a life-threatening ventricular tachyarrhythmia in a participant with an ICD immediately before death, regardless of the therapy delivered by the ICD. Sudden death was defined as unexpected death immediately after the onset of symptoms, but in the absence of an electrogram recording during the event (for example if a patient with an ICD was cremated without obtaining the data). The baseline characteristics of the participants were evaluated and the Kaplan-Meier method was used to compare the incidences of the listed clinical events between the two groups. Multivariate Cox proportional hazards regression analysis was used to identify risk factors for AF.

Statistical analysis

Categorical data are presented as absolute counts and percentages, and continuous data as means ± standard deviations. When two groups were compared, we used the $\chi 2$ test for categorical variables and Student's *t*-test for continuous variables. Cumulative event rates (all-cause mortality, ES, hospitalization, appropriate device therapy, and inappropriate device therapy) were analyzed using the Kaplan-Meier method, and log-rank tests were used to test statistical hypotheses. The effect of AF on mortality was assessed using a Cox regression model that was adjusted for AF, age, LVEF, secondary or primary indication, and the use of beta-blockers and/or a class III antiarrhythmic drug, and hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated.

Results

Baseline characteristics

Data from 1549 patients who enrolled in the Nippon Storm Study at 48 ICD centers in Japan were analyzed. The baseline characteristics of these participants are summarized in Table 1. Comparisons of the AF group (n = 257, 16.6%) and the non-AF group (n = 1292, 83.4%) showed that participants in the former were older (67.7 *vs.* 61.4 years; $p<0.0001$); and had more primary indications (54.1% vs. 45.8%; p = 0.003), lower LVEF (38.0 ± 17.0% vs. 43.5 ± 18.9%; $p<0.0001$), lower eGFR (51.7 ± 20.8 vs. 62.2 ± 26.6; $p<0.0001$), had more incidence of DCM (30.4% vs 21.4%; p = 0.003), and more hypertension (47.5% vs 37.7%; p = 0.004), hyperuricemia (17.9% vs 10.8%; p = 0.002), and cerebral infarction (14.0% vs 5.3%; $p<0.0001$). Although there were no significant differences in the prevalence of other underlying structural heart diseases between the two groups [AF group: IHD in 31.9% (82/257) and HCM in 14.8% (38/257) vs. non-AF group: IHD in 31.3% (404/1292) and HCM in 12.6% (163/1310)], primary electrical abnormalities (including long QT syndrome, Brugada syndrome, and idiopathic ventricular fibrillation) were more frequent in the non-AF group [4.7% (12/257) vs. 18.3% (236/1292); $p<0.001$].

Mortality and cause of death

During a median follow-up period of 28 months, the mortality rate of the AF group was significantly higher than that of the non-AF group [41/257 (16.0%) vs. 103/1292 (8.0%), log-rank $p<0.0001$) (Fig. 1). In multivariate analysis that included AF, LVEF, age, secondary prevention, and the use of a beta-blocker or class III antiarrhythmic agent, AF was significantly associated with all-cause mortality (p = 0.013; HR=1.62) (Table 2). The incidences of death due to HF or arrhythmia, and sudden death were significantly higher in the AF group than in the non-AF group [15/257 (5.8%) vs. 30/1310 (2.3%); p = 0.005, 7/257 (2.7%) vs. 6/1292 (0.46%); p = 0.002; respectively]. However, the incidence of non-cardiac death did not significantly differ between the two groups [19/257 (7.4%) in the AF group vs. 67/1292 (5.2%) in the non-AF group; p = 0.17] (Table 3). The incidence of ES also did not significantly differ between the two groups [21/257 (8.2%) in the AF group vs. 76/1292 (5.9%) in the non-AF group; p = 0.13] (Fig. 2a).

Table 1
Comparisons of the characteristics of the AF group (n = 257, 16.6%) and the non-AF group (n = 1292, 83.4%).
AF, atrial fibrillation; EF, ejection fraction; NYHA, New York Heart Association; CRT-D, cardiac resynchronization therapy defibrillator; LQT, long QT; IVF, idiopathic ventricular fibrillation; OMI, old myocardial infarction; IHD, ischemic heart disease; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; PAD, peripheral atrial disease; BNP, brain natriuretic peptide; Hb, hemoglobin; AAD, anti-arrhythmic drug.

	AF group (n = 257)	Non-AF group (n = 1292)	p
Age (years)	67.7 ± 10.9	61.4 ± 14.6	<0.0001
Male	215 (83.7%)	994 (76.9%)	0.0167
EF	38.0 ± 17.0	43.5 ± 18.9	<0.0001
Primary prevention	139 (54.1%)	592 (45.8%)	0.016
No atrial lead	56 (21.8%)	145 (11.2%)	<0.0001
NYHA(n)	I(65) II()94 III(86) IV(12)	I(572)II(398)III(282)IV(40)	
NYHAIII+IV	98(38.1%)	322(24.9%)	<0.0001
CRT-D	115 (44.7%)	391 (30.2%)	<0.0001
LQT+Brugada+IVF	12 (4.7%)	236 (18.3%)	<0.0001
OMI+IHD	82 (31.9%)	404 (31.3%)	0.88
DCM	78 (30.4%)	276 (21.4%)	0.003
HCM	38 (14.8%)	163 (12.6%)	0.36
ARVC	2 (0.8%)	26 (2.0%)	0.14
Cardiac sarcoidosis	0	61 (4.7%)	<0.0001
Hypertension	122(47.5%)	487(37.7%)	0.004
Diabetes	82(31.9%)	313(24.2%)	0.11
Dyslipidemia	53(20.6%)	370(28.6%)	0.009
PAD	5(2.0%)	27(2.1%)	1.00
Hyperuricemia	46(17.9%)	140(10.8%)	0.002
Cerebral infarction	36(14.0%)	69(5.3%)	<0.0001
Cerebral hemorrhage	3(1.17%)	14(1.08%)	0.90
Heart Rate (bpm)	69.9 ± 18.6	65.4 ± 13.3	<0.0001
QRS width	130.3 ± 35.4	126.1 ± 35.4	0.08
QT interval	434.4 ± 61.4	441.9 ± 108.9	0.28
BNP	522.0 ± 572.8	425.3 ± 764.0	0.07
Hb	13.0 ± 2.1	13.9 ± 25.6	0.59
Cr	1.39±1.24	1.27±1.53	0.26
eGFR	51.7 ± 20.8	62.2 ± 26.6	<0.0001
Class III AAD	115 (44.8%)	452 (35.0%)	0.004
β-blocker	162 (63.0%)	713 (55.2%)	0.02

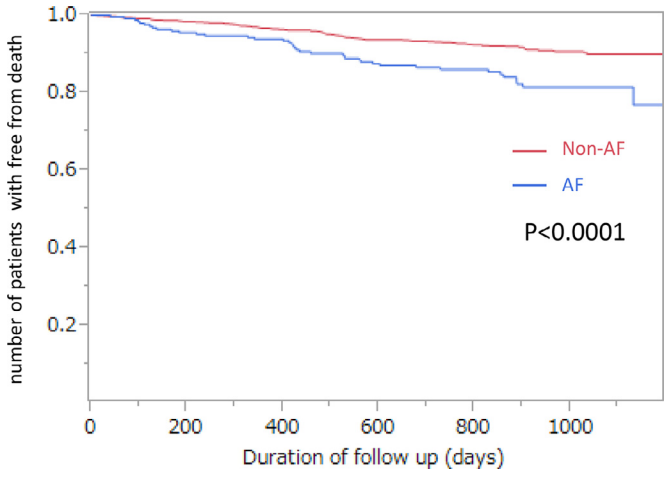

Fig 1. Kaplan-Meier curves for all-cause mortality in participants in the non-AF and AF groups.
Log rank test: p<0.0001. Red: non-AF group; blue: AF group.
AF, atrial fibrillation.

Table 2
Hazard ratios for all-cause mortality associated with clinical variables.
AF, atrial fibrillation; EF, ejection fraction; AAD, anti-arrhythmic drug.

	Hazard ratio	95% CI	p
AF	1.62	1.10–2.32	0.013
EF < 42%	2.21	1.50–3.37	<0.0001
Secondary prevention	1.04	0.73–1.49	0.82
Age (10-year increments)	1.55	8.64–107.4	<0.0001
β-blocker	0.84	0.59–1.17	0.32
Class III AAD	1.18	0.83–1.70	0.36

Table 3
Comparison of the causes of death in the two groups.
AF, atrial fibrillation.

	AF group (n = 257)	Non-AF group (n = 1292)	p
Cardiac death	22 (8.6%)	36 (2.8%)	<0.001
Heart failure	15 (5.8%)	30 (2.3%)	0.005
Arrhythmia and sudden death	7 (2.7%)	6 (0.46%)	0.002
Non-Cardiac death	19 (7.4%)	67 (5.2%)	0.17
Cancer	2 (0.8%)	12 (0.9%)	1.00
Infection	4 (1.6%)	11 (0.9%)	0.29
Hemorrhage	0	2 (0.15%)	0.39
Unknown/other	13 (5.0%)	42 (3.2%)	0.17

Hospitalization

Patients in the AF group had a significantly higher incidence of hospitalization than those in the non-AF group (53/257 in the AF group vs. 141/1292 in the non-AF group; p<0.0001) (Fig. 2b). In multivariate analysis that included AF, LVEF, age, secondary prevention, and the use of a beta-blocker or class III anti-arrhythmic drug, AF was only the parameter that was significantly associated with hospitalization (p = 0.0004; HR 1.87).

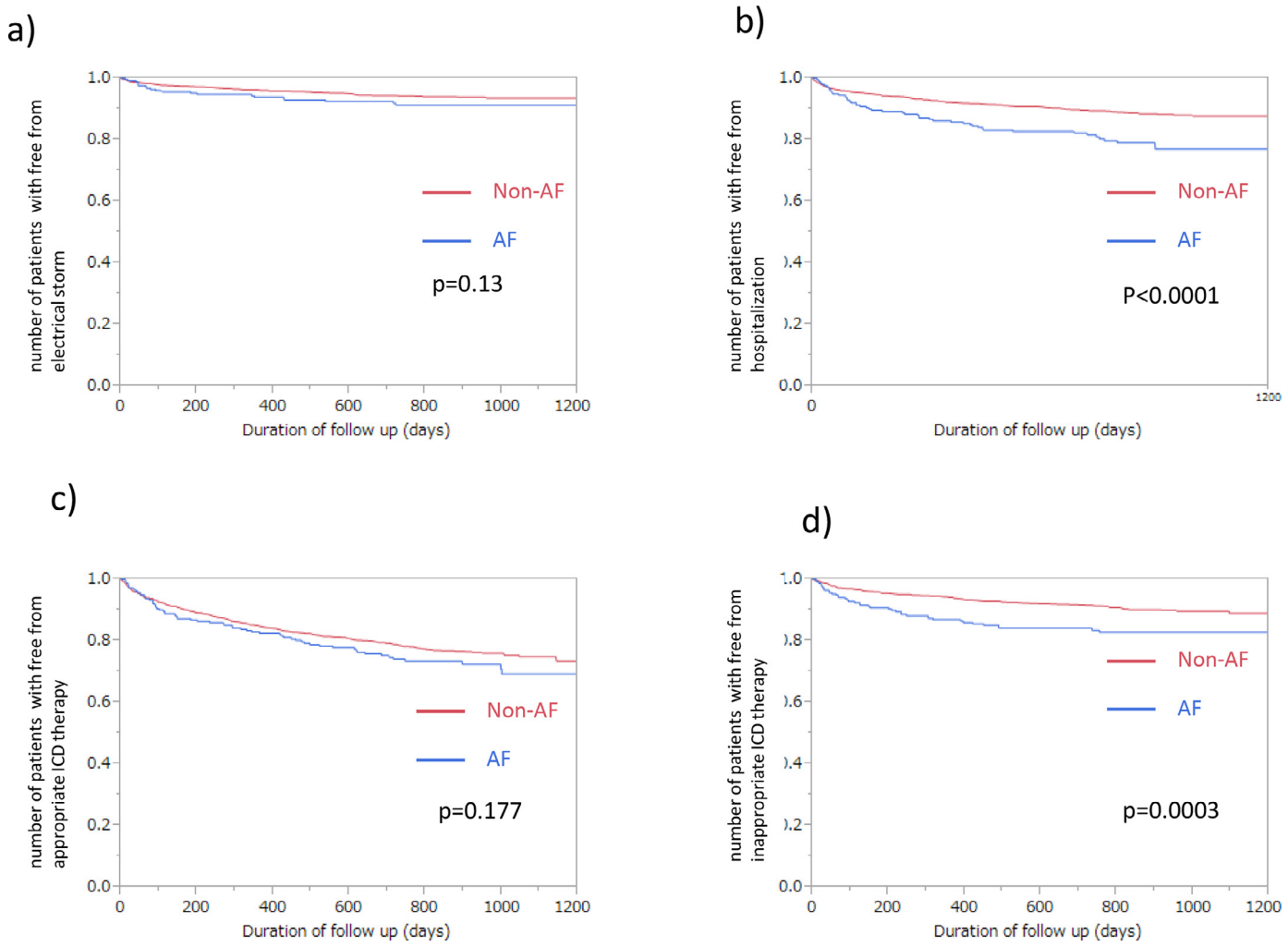

Fig 2. Kaplan-Meier analyses of events during the follow-up period in each group.
(a) Electrical storm events, $p = 0.13$. (b) Hospitalization, $p<0.0001$. (c) Appropriate ICD therapy, $p = 0.177$. (d) Inappropriate ICD therapy, $p = 0.0003$. Red: non-AF group; blue: AF group.
AF, atrial fibrillation.

Appropriate and inappropriate ICD therapy

Although the cumulative event rate for appropriate ICD therapy in the AF group did not significantly differ from that in the non-AF group [65/257 (25.3%) vs. 286/1292 (22.1%), $p = 0.29$], the event rate for inappropriate therapy in the AF group was significantly higher than that in the non-AF group [40/257 (15.6%) vs. 115/1292 (8.9%), $p = 0.002$, respectively] (Fig. 2c and d). In multivariate analysis that included AF, LVEF, age, the use of a beta-blocker or class III anti-arrhythmic drug, and secondary prevention, AF was significantly associated with increase of inappropriate ICD therapy ($p<0.0001$, HR=2.25), and classIIIanti-arrhythmic drug was associated with decrease of inappropriate ICD therapy ($p = 0.03$, HR=0.67) (Table 4). Furthermore, supraventricular tachycardia, including AF, was the main cause of inappropriate ICD shock therapy in both groups, but this occurred more frequently in the AF group than in the non-AF group [21/22 (95.1%) vs. 32/51 (62.7%)].

Table 4
Hazard ratios for the risks of inappropriate ICD therapy associated with clinical variables
AF, atrial fibrillation; EF, ejection fraction; AAD, anti-arrhythmic drug.

	Hazard ratio	95% CI	*p*
AF	2.25	1.54–3.26	<0.0001
EF < 42%	1.20	0.84–1.72	0.31
Secondary prevention	1.32	0.94–1.87	0.11
Age (10-year increments)	0.49	0.21–1.17	0.11
β-blocker	1.02	0.73–1.43	0.89
Class III AAD	0.67	0.45–0.96	0.03

Discussion

The principal novel finding of the present study is that a history of AF at the time of ICD or CRT-D implantation is an independent risk factor for mortality resulting from HF or arrhythmia in Japanese patients.

Mortality

It is well known that the incidence of AF increases as HF worsens, and its existence is a major cause of further deterioration of HF and fatal cardiac arrhythmia. A significant negative impact on the prognosis of HF patients has also been shown by the CASTLE AF study [6], which demonstrated that the elimination or reduction of AF reduced mortality in patients with LVEF <35%. Because the majority of patients with ICD or CRT-D have poor LV systolic function, AF may have a significant impact on the outcomes of these patients. According to this study, class III anti-arrhythmic drugs re-

duced the incidence of inappropriate therapy, but it could not provide improvement in mortality. Therefore, challenges to restore sinus rhythm by performing catheter ablation of AF should be considered for patients with reduced LVEF as the CASTLE AF suggested [6]. However, the impact of AF on the prognosis of patients with ICD or CRT-D has been controversial. van Gelder et al. showed no significant difference in mortality between patients with AF and those without in a retrospective study of patients with ICD [2], whereas Bunch et al. demonstrated that persistent AF is an independent risk factor for overall mortality during the first year of ICD therapy [3]. The findings of the present study are consistent with the latter finding, because they show that the total mortality rate in the AF group was 1.62 times higher than that in the non-AF group. Analysis of the cause of death showed that death due to HF and sudden cardiac death were significantly more common in the AF group than in the non-AF group.

Several previous clinical studies have demonstrated that the loss of atrioventricular synchrony and impairment in optimal biventricular pacing during AF induce HF in patients with low LVEF who have ICD or CRT-D [7,8]. The loss of synchronous pacing in CRT-D patients due to AF is thought to be one of the causes of HF in the present study. Although the causes of hospitalization were not collected in the present study, we speculate that 53.6% of the hospitalization events were related to ICD therapy, because they occurred immediately after ICD therapy (inappropriate therapy in 22 participants, appropriate therapy in 81 participants, and both therapies in one participant). Infection associated with the device was another apparent cause of hospitalization ($n = 14$).

Irregular RR interval during AF may cause random impulse attacks or short-long-short sequences in a reentrant pathway, and may ultimately induce VT or VF. AF may also induce a reduction in cardiac output and an increase in filling pressure, because of the loss of atrial effective contraction, which are likely to induce myocardial ischemia [9].

Recent clinical trials have shown that shock ICD therapies (either appropriate or inappropriate) impair the patient's QOL and increase mortality. In the present study, the incidence of sudden death in the AF group was significantly higher than that in the non-AF group, even though all the patients had devices implanted. Of the 13 participants (6 patients in AF group and 7 patients in Non-AF group) who died because of arrhythmia, clinical data (stored electrograms in the ICDs) immediately before the event were available for six. Based on the detailed analysis of the electrograms, multiple appropriate but unsuccessful shocks, including ES, were observed in 5/6 participants (4/7 in AF group and 1/6 in Non-AF group), but four of them died the day after the arrhythmic event. Another patient died due to the failure to appropriately detect VT. Although it is not clear how the presence of AF was associated with death due to arrhythmia in these patients, irregular and short RR intervals may have led to subsequent VT or VF, or the setting of a high threshold to avoid the administration of inappropriate therapy may have caused VT/VF to be missed.

Inappropriate therapy

In addition to the present study, many previous studies have shown that AF, and especially paroxysmal AF, is associated with inappropriate ICD therapy [10]. Even when the most advanced algorithms are used to differentiate supra-ventricular tachycardia from VT/VF, AF is still the commonest cause of inappropriate therapy [11], because it may cause a rapid heart rate, which reaches the detection rate of VT/VF, especially in the presence of HF. Rapid AF produces relatively regular RR interval and aberrant ventricular conduction, which finally results in diagnostic error and inappropriate therapy. The delivery of inappropriate shock therapy during the development of HF may have a deleterious effect on the patient and increase the risk of mortality.

Limitations

There were several limitations to the present study. First, we could not collect follow-up data regarding the development of AF after ICD implantation. Therefore, the new onset of AF after ICD implantation, which has been reported to largely affect patients' outcomes, could not be evaluated in the present study. However, the main purpose of our study is to speculate whether existence of AF at the time of implantation affects outcome of ICD patients with AF. Second, in 81/257 (31.5%) patients with AF, we could not exactly differentiate the type of AF, such as paroxysmal or permanent. Several previous studies have demonstrated that paroxysmal AF is associated with a higher prevalence of inappropriate therapy [3], but we could not find any difference regarding inappropriate therapy or mortality rate between patients with paroxysmal and those with permanent AF by excluding patients with undetermined type of AF. Therefore, the types of AF might not have largely influenced the patient outcomes in the present study. Third, the appropriateness of the ICD therapies except for electrical storm were judged by the attending medical doctors. Two electrophysiologists, who did not participate in the Nippon storm study, independently evaluated whether the events of "electrical storm" fulfilled the criteria of ES by analyzing the stored electrograms. According to this evaluation, 35 out of 179 events were excluded from the main analysis of ES because of unsatisfied criteria, however the accuracy of differentiation of VT or VF from supra-ventricular tachycardia determined by the attending doctors was extremely high [176 out of 179 events (98.3%)]. Therefore, we considered that almost all the events were diagnosed correctly in this study. Furthermore, the rate of inappropriate therapy depends on device programing and manufacturers, which is not integrated in each institution.

Conclusion

AF carries an independent 1.62-fold higher risk of death and a 2.25-fold risk of inappropriate therapy after ICD implantation. To manage the ICD patients with AF, a particular ICD programming to avoid inappropriate therapy (e.g. delayed or high-rate therapy) or catheter ablation to improve the mortality are recommended.

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Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request for anyone within a year since the paper is published. Only raw patient data are available and any type of analysis will send the data through e-mail with fine explanations if anyone contacts me by email.

Disclosures

Takashi Nitta is a member of the editorial team of *Circulation Journal*.

IRB information

Ethics Committee, Kindai University Faculty of Medicine granted an exemption from requiring ethics approval.

References

[1] Kobe J, Wasmer K, Andresen D, Kleemann T, Spitzer SG, Jehle J. Impact of atrial fibrillation on early complications and one year-survival after cardioverter defibrillator implantation: results from the German device registry. Int J Cardiol 2013;168:4184–90.
[2] van Gelder IC, Phan HM, Wilkoff BL, Brown ML, Rogers T, Peterson BJ. Prognostic significance of atrial arrhythmias in a primary prevention ICD population. Pacing Clin Electrophysiol 2011;34:1070–9.
[3] Bunch TJ, Day JD, Olshansky B, Stolen KQ, Mullin CM. Newly detected atrial fibrillation in patients with an implantable cardioverter-defibrillator is a strong risk marker of increased mortality. Heart Rhythm 2009;6:2–8.
[4] Noda T, Kurita T, Nitta T, Chiba Y, Furushima H, Matsumoto N. Significant impact of electrical storm on mortality in patients with structural heart disease and an implantable cardiac defibrillator. Int J Cardiol 2018;255:85–91.
[5] Kurita T, Noda T, Nitta T, Furushima H, Shimizu A, Ohe T. Nippon Storm Study design. J. Arrhythmia 2012;28:277–9.
[6] Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L. Catheter ablation for atrial fibrillation with heart failure. N Engl J Med 2018;378:417–27.
[7] Gasparini M, Auricchio A, Metra M, Regoli F, Fantoni C, Lamp B. Long-term survival in patients undergoing cardiac resynchronization therapy: the importance of performing atrio-ventricular junction ablation in patients with permanent atrial fibrillation. Eur Heart J 2008;29:1644–52.
[8] Upadhyay GA, Choudhry NK, Auricchio A, Ruskin J, Singh JP. Cardiac resynchronization in patients with atrial fibrillation: a meta-analysis of prospective cohort studies. J Am Coll Cardiol 2008;52:1239–46.
[9] Takigawa M, Noda T, Kurita T, Aihara N, Yamada Y, Okamura H. Predictors of electrical storm in patients with idiopathic dilated cardiomyopathy–how to stratify the risk of electrical storm. Circ J 2010;74:1822–9.
[10] Daubert JP, Zareba W, Cannom DS, McNitt S, Rosero SZ, Wang P. Inappropriate implantable cardioverter-defibrillator shocks in MADIT II: frequency, mechanisms, predictors, and survival impact. J Am Coll Cardiol 2008;51:1357–65.
[11] Auricchio A, Schloss EJ, Kurita T, Meijer A, Gerritse B, Zweibel S. Low inappropriate shock rates in patients with single- and dual/triple-chamber implantable cardioverter-defibrillators using a novel suite of detection algorithms: painFree SST trial primary results. Heart Rhythm 2015;12:926–36.