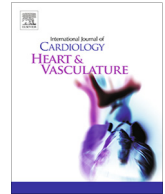




Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.journals.elsevier.com/ijc-heart-and-vasculature

Risk factors for the first and second inappropriate implantable cardioverter-defibrillator therapy



Nobuhiro Nishii^{a,*}, Takashi Noda^b, Takashi Nitta^c, Yoshifusa Aizawa^d, Tohru Ohe^e, Takashi Kurita^f

^a Department of Cardiovascular Therapeutics, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan

^b Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan

^c Department of Cardiovascular Surgery, Nippon Medical School, Tokyo, Japan

^d Department of Research and Development, Tachikawa Medical Center, Niigata, Japan

^e Okayama City Hospital, Okayama, Japan

^f Department of Internal Medicine, Faculty of Medicine, Kindai University, Osaka-Sayama, Japan

ARTICLE INFO

Article history:

Received 7 February 2021

Received in revised form 31 March 2021

Accepted 1 April 2021

Keywords:

Nippon storm study

Implantable cardioverter-defibrillator

Cardiac resynchronization therapy with defibrillator

Inappropriate ICD therapy

ABSTRACT

Introduction: Various risk factors for the first inappropriate implantable cardioverter-defibrillator (ICD) therapy event have been reported, including a history of atrial fibrillation/atrial flutter (AF/AFL), younger age, and multiple zones. Nonetheless, which factors are concordant with real-world data has not been clarified, and risk factors for the second inappropriate ICD therapy event have not been well examined. This study aimed to clarify the risk factors for the first and second inappropriate ICD therapy events.

Methods: We conducted a post-hoc secondary analysis of data from a multicenter, prospective observational study (the Nippon Storm Study) designed to clarify the risk factors for electrical storm.

Results: The analysis included data from 1549 patients who received ICD or cardiac resynchronization therapy with defibrillator (CRT-D). Over a median follow-up of 28 months, 293 inappropriate ICD therapy events occurred in 153 (10.0%) patients. On multivariate Cox regression analysis, the risk factors for the first inappropriate ICD therapy event were younger age (hazard ratio [HR], 0.986; $p = 0.028$), AF/AFL (HR, 2.324; $p = 0.002$), ICD without CRT implantation (HR, 2.377; $p = 0.004$), and multiple zones (HR, 1.852; $p = 0.010$). “No-intervention” after the first inappropriate ICD therapy event was the sole risk factor for the second inappropriate ICD therapy event.

Conclusions: Risk factors for the first inappropriate ICD therapy event were similar to those previously reported. Immediate intervention after the first inappropriate ICD therapy event could reduce the risk of the second inappropriate event.

© 2021 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Implantable cardioverter-defibrillator (ICD), including cardiac resynchronization therapy with defibrillator (CRT-D), has become an established therapeutic option for the primary and secondary prevention of sudden arrhythmic death via treatment of ventricular tachyarrhythmias [1–3]. However, it is known that some

patients receive inappropriate ICD therapy for sinus tachycardia, atrial tachycardia, atrial fibrillation (AF), atrial flutter (AFL), T-wave oversensing, or nonphysiological noise. Furthermore, inappropriate ICD-delivered shocks can cause anxiety and death [4–7]. Since the publication of early ICD trials [1–3], there have been significant advances in ICD technology as well as substantial changes in device programming to lower the risk of inappropriate ICD therapy [8–10]. Although the risk factors for the first inappropriate ICD therapy event have been reported [11–14], patients in daily practice may substantially differ from those included in pivotal trials. This raises the question as to whether risk factors for the first inappropriate ICD therapy event are the same as those previously reported. Additionally, the management after the first inappropriate ICD therapy event seems to be important to prevent the second inappropriate ICD therapy event; however, this has not been well

Abbreviations: AF/AFL, atrial fibrillation/atrial flutter; ATP, antitachycardia pacing; CRT-D, cardiac resynchronization therapy with defibrillator; ICD, implantable cardioverter-defibrillator; VF, ventricular fibrillation; VT, ventricular tachycardia; LVEF, left ventricular ejection fraction; IQR, interquartile range; SD, standard deviation.

* Corresponding author at: Department of Cardiovascular Therapeutics, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan.

E-mail address: nnishi@md.okayama-u.ac.jp (N. Nishii).

<https://doi.org/10.1016/j.ijcha.2021.100779>

2352-9067/© 2021 The Authors. Published by Elsevier B.V.

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

examined. The Nippon Storm Study [15] is a multicenter, prospective observational study investigating electrical storm events. In 1570 patients who received ICD or CRT-D, the incidence rate of electrical storm was 6.6% (84 of 1570 patients) over a median follow-up of 28 months. The present study aimed to clarify the risk factors for the first and second inappropriate ICD therapy events among patients enrolled in the Nippon Storm Study.

2. Methods

2.1. Study population

The present study is a post-hoc secondary analysis of patients enrolled in the Nippon Storm Study. The design and primary results of the Nippon Storm Study have been published [15,16]. Briefly, the Nippon Storm Study was organized by the Japanese Heart Rhythm Society and the Japanese Society of Electrophysiology. Web-based registration of patients was conducted in 48 Japanese ICD centers (see Appendix), with the Japanese Heart Rhythm Society collecting data from the physicians who input patients' data. All 1570 patients provided their written informed consent, and the study protocol was approved by the Institutional Review Board and/or Medical Ethics Committee of each center.

2.2. ICD programming

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. In most patients, the ventricular fibrillation (VF) zone was >188–220 bpm, with at least one train of antitachycardia pacing (ATP) before the ICD-delivered shock, and the ventricular tachycardia (VT) zone was >140–180 bpm, with at least three trains of ATP before the ICD-delivered shock, although modifications were permitted based on each patient's background. The single zone included only a VF zone, and multiple zones included both VF and VT zones.

2.3. Follow-up

To provide a precise follow-up, we constructed a new tracking system, the "Chaser," which was intended to minimize the loss of follow-up data. Intervention data (both appropriate and inappropriate ICD therapy) were sent to the office of the Japanese Heart Rhythm Society, using a dedicated website, at a maximum interval of 6 months. The ICD therapeutic interventions were classified into ATP, low-energy shocks, and high-energy shocks.

The following baseline patient characteristics were assessed: age, sex, underlying heart disease, indication of ICD (primary or secondary), and complications related to the implantation procedure. An inappropriate ICD therapy was defined as any inappropriate ATP or ICD shock for sinus tachycardia, AF/AFL, regular supraventricular tachycardia, or non-arrhythmic events (such as detected noise, myopotentials, electromagnetic interference, and T-wave oversensing). The primary outcome of our study was the incidence rate and the risk factors for the first and second inappropriate ICD therapy events. The time period between the first and second inappropriate ICD therapy events was also included in the analysis. Inappropriate ICD therapy episodes occurring incessantly or during short periods of fewer than 6 h were regarded as the first inappropriate ICD therapy event, not as the second or third inappropriate ICD therapy event.

2.4. Statistical analysis

Baseline characteristics were evaluated between patients with and without inappropriate ICD therapy. Continuous data were reported as a mean \pm standard deviation (SD), or median and interquartile range (IQR), as appropriate for the data distribution, with between-group differences evaluated using Student's *t*-test or the Wilcoxon's rank-sum test. Categorical data were summarized as frequencies and percentages, with between-group differences compared using Pearson's chi-squared test. The 95% confidence intervals (CI) for the proportion of lead failures detected by arrhythmic events were also calculated. Between-group differences in the time-to-detection (reported as a mean \pm SD or median and IQR, as appropriate for the distribution of data) were evaluated using Student's *t*-test or Wilcoxon's rank-sum test. Cumulative probability of inappropriate ICD therapy rate was reported using the Kaplan-Meier method, with between-group differences in the cumulative event rate evaluated using the log-rank test. Multivariate Cox proportional hazards regression analysis was conducted to identify the independent risk factors for the first and second inappropriate ICD therapy events. All tests were two-sided, and a *p*-value <0.05 was considered statistically significant. All statistical analyses were performed using R software version 3.4.2 (R Project for Statistical Computing).

3. Results

3.1. Patient characteristics

Among 1570 patients enrolled in the Nippon Storm Study from 48 ICD centers in Japan, data on inappropriate ICD therapies were not available for 21 patients, while the data of the remaining 1549 patients were included in our analysis. The baseline characteristics of these 1549 patients are summarized in Table 1. At the time of implantation, the average age of patients was 62.5 years, with 1209 (78.1%) patients being men. An ICD was implanted in 1048 (67.7%) patients, with CRT-D used in the other 501 (32.3%) patients. The median left ventricular ejection fraction (LVEF) before implantation was 38%, with ICD indicated for major causes of structural heart disease, namely ischemic heart disease in 486 (31.4%) patients and dilated cardiomyopathy (DCM) in 347 (22.4%). Patient characteristics based on device type (ICD or CRT-D) are also presented in Table 1.

3.2. Inappropriate ICD therapy

Over a median follow-up of 28 months, 293 inappropriate ICD therapy events occurred in 153 out of 1549 (10.0%) patients. The causes of inappropriate ICD therapy were sinus tachycardia in 35 events, atrial tachyarrhythmia in 175 events, T-wave oversensing in 7 events, electromagnetic interference in 1 event, myopotential in 1 event, and not available in 74 events.

3.3. Risk factors for the first inappropriate ICD therapy

The Kaplan-Meier curve indicated that the cumulative rate of inappropriate ICD therapy events was 6.9% at 12 months (Fig. 1A). Differences between baseline characteristics of patients with and without the first inappropriate ICD therapy event are described in Table 1. No between-group differences in the distribution of sex, age, symptoms of heart failure, LVEF, baseline heart rate or medication were identified. However, patients with AF/AFL were significantly more likely to receive inappropriate ICD therapy than those without AF/AFL (inappropriate ICD therapy; 15.8% vs. 9.4%, *p* = 0.003). The incidence rate of inappropriate ICD therapy was

Table 1
Patient characteristics based on the first inappropriate ICD therapy.

| | Total | Inappropriate ICD therapy (-) | Inappropriate ICD therapy (+) | p | ICD | CRT-D | p |
|-------------------------------------|--------------|-------------------------------|-------------------------------|--------|--------------|--------------|--------|
| N | 1549 | 1396 | 153 | | 1048 | 501 | |
| Male, n (%) | 1209 (78.1) | 1095 (78.4) | 114 (74.5) | 0.312 | 828 (79.0) | 379 (75.6) | 0.195 |
| Age, years | 62.5 (14.2) | 62.7 (13.9) | 60.2 (16.4) | 0.039 | 60.7 (15.2) | 66.1 (11.0) | <0.001 |
| Heart disease, n (%) | | | | 0.099 | | | <0.001 |
| Ischemic heart disease | 486 (31.4) | 449 (32.2) | 37 (24.2) | | 340 (32.4) | 146 (29.1) | |
| Dilated cardiomyopathy | 347 (22.4) | 312 (22.3) | 35 (22.9) | | 111 (10.6) | 236 (47.1) | |
| Hypertrophic cardiomyopathy | 195 (12.6) | 171 (12.2) | 24 (15.7) | | 167 (15.9) | 28 (5.6) | |
| ARVC | 30 (1.9) | 25 (1.8) | 5 (3.3) | | 25 (2.4) | 5 (1.0) | |
| Cardiac sarcoidosis | 61 (3.9) | 58 (4.2) | 3 (2.0) | | 58 (4.2) | 3 (2.0) | |
| Brugada syndrome | 135 (8.7) | 125 (9.0) | 10 (6.5) | | 135 (12.9) | 0 (0.0) | |
| Ideopathic ventricular fibrillation | 80 (5.2) | 70 (5.0) | 10 (6.5) | | 80 (7.6) | 0 (0.0) | |
| Others | 215 (13.9) | 186 (13.3) | 29 (19.0) | | 132 (12.6) | 87 (17.4) | |
| Primary prevention, n (%) | 731 (47.2) | 666 (47.7) | 65 (42.5) | 0.253 | 369 (35.2) | 362 (72.3) | <0.001 |
| Secondary prevention, n (%) | 818 (52.8) | 730 (52.3) | 88 (57.5) | | 679 (64.8) | 139 (27.7) | |
| Type of CIED, n (%) | | | | <0.001 | | | <0.001 |
| ICD | 1048 (67.7) | 921 (66.0) | 127 (83.0) | | - | - | |
| CRT-D | 501 (32.3) | 475 (34.0) | 26 (17.0) | | - | - | |
| Single chamber, n (%) | 329 (21.2) | 290 (20.8) | 39 (25.5) | 0.211 | 271 (25.9) | 61 (12.2) | <0.001 |
| NYHA class, n (%) | | | | 0.102 | | | <0.001 |
| I | 637 (41.1) | 567 (40.6) | 70 (45.8) | | 617 (58.9) | 20 (4.0) | |
| II | 492 (31.8) | 438 (31.4) | 54 (35.3) | | 330 (31.5) | 162 (32.3) | |
| III | 368 (23.8) | 344 (24.6) | 24 (15.7) | | 95 (9.1) | 273 (54.5) | |
| IV | 52 (3.4) | 47 (3.4) | 5 (3.3) | | 6 (0.6) | 46 (9.2) | |
| Ejection fraction, % | 42.6 (18.7) | 42.3 (18.6) | 45.0 (19.3) | 0.090 | 49.5 (18.1) | 27.0 (9.4) | <0.001 |
| Log BNP | 2.2 (0.7) | 2.2 (0.7) | 2.2 (0.7) | 0.773 | 2.0 (0.7) | 2.6 (0.5) | <0.001 |
| Serum creatinine, mg/dl | 1.3 (1.5) | 1.3 (1.4) | 1.3 (2.0) | 0.911 | 1.2 (1.2) | 1.6 (2.0) | <0.001 |
| Atrial rhythm, n (%) | | | | 0.003 | | | <0.001 |
| Sinus rhythm | 1256 (81.1) | 1137 (81.4) | 119 (77.8) | | 915 (87.3) | 341 (68.1) | |
| Atrial fibrillation/Atrial flutter | 190 (12.3) | 160 (11.5) | 30 (19.6) | | 100 (9.5) | 90 (18.0) | |
| Others | 103 (6.6) | 99 (7.1) | 4 (2.6) | | 33 (3.1) | 70 (14.0) | |
| Heart rate | 66.3 (14.2) | 66.1 (14.2) | 67.5 (14.5) | 0.253 | 64.9 (13.1) | 69.0 (15.9) | <0.001 |
| QRS duration, ms | 126.9 (35.2) | 128.1 (35.7) | 116.4 (28.9) | <0.001 | 112.8 (27.0) | 156.2 (32.4) | <0.001 |
| QT interval, ms | 440.1 (57.2) | 441.1 (57.6) | 431.2 (52.9) | 0.042 | 431.1 (57.0) | 462.1 (57.0) | <0.001 |
| Death, % | 144 (9.3) | 134 (9.6) | 10 (6.5) | 0.275 | 76 (7.3) | 68 (13.6) | <0.001 |
| Inappropriate ICD therapy, % | - | - | - | - | 127 (12.1) | 26 (5.2) | <0.001 |
| Comorbidity, n (%) | | | | | | | |
| Hypertension | 609 (39.3) | 546 (39.1) | 63 (41.2) | 0.682 | 417 (39.8) | 192 (38.3) | 0.617 |
| Diabetes mellitus | 395 (25.5) | 375 (26.9) | 20 (13.1) | <0.001 | 230 (21.9) | 165 (32.9) | <0.001 |
| Dyslipidemia | 423 (27.3) | 387 (27.7) | 36 (23.5) | 0.313 | 296 (28.2) | 127 (25.3) | 0.247 |
| Cerebral infarction | 105 (6.8) | 96 (6.9) | 9 (5.9) | 0.768 | 69 (6.6) | 36 (7.2) | 0.666 |
| Cerebral hemorrhage | 17 (1.1) | 16 (1.1) | 1 (0.7) | 0.884 | 12 (1.1) | 5 (1.0) | 1.000 |
| Peripheral artery disease | 32 (2.1) | 30 (2.1) | 2 (1.3) | 0.692 | 20 (1.9) | 12 (2.4) | 0.568 |
| Medication, n (%) | | | | | | | |
| Beta blocker | 875 (56.5) | 793 (56.8) | 82 (53.6) | 0.500 | 534 (51.0) | 341 (68.1) | <0.001 |
| ACE-I | 440 (28.4) | 397 (28.4) | 43 (28.1) | 1.000 | 247 (23.6) | 193 (38.5) | <0.001 |
| ARB | 421 (27.2) | 377 (27.0) | 44 (28.8) | 0.714 | 256 (24.4) | 165 (32.9) | <0.001 |
| Class III antiarrhythmic drugs | 520 (33.6) | 480 (34.4) | 40 (26.1) | 0.050 | 345 (32.9) | 175 (34.9) | 0.455 |
| Program | | | | | | | |
| Single zone, n (%) | 428 (28.5) | 397 (29.4) | 31 (20.4) | 0.025 | 328 (31.3) | 23.4 (20.0) | <0.001 |
| Multiple zones, n (%) | 1074 (71.5) | 953 (70.6) | 121 (79.6) | | 720 (68.7) | 401 (80.0) | |
| minimum cut-off rate, bpm | 166.2 (24.4) | 166.7 (24.5) | 161.5 (22.9) | 0.013 | 168.3 (25.3) | 161.5 (21.6) | <0.001 |

Values are mean (standard deviation), median [interquartile range] or number (%) of patients.

ARVC denotes arrhythmogenic right ventricular cardiomyopathy, NYHA New York Heart Association, BNP brain natriuretic peptide.

ICD denotes implantable cardioverter defibrillator, CRT-D cardiac resynchronization therapy with defibrillator.

ACE-I denotes angiotensin converting enzyme inhibitor, ARB angiotensin receptor, bpm beat per minute.

significantly greater in the ICD group than in the CRT-D group (12.1% vs. 5.1%, $p < 0.001$). The baseline QRS width and QT interval were significantly shorter in patients who received inappropriate ICD therapy than those who did not (QRS width: 120 vs. 110 ms, respectively, $p < 0.001$; QT interval: 438 vs. 420 ms, respectively, $p = 0.027$). The incidence of inappropriate ICD therapy was greater in patients treated using multiple zones than in those treated using a single zone (11.2% vs. 7.2%, $p = 0.025$). The minimum cut-off rate was significantly lower in patients who received inappropriate ICD therapy than those who did not (161.5 vs. 168.3 bpm, $p < 0.001$).

On multivariate Cox regression analysis, younger age (hazard ratio [HR], 0.986; 95% CI, 0.973–0.998; $p = 0.028$), AF/AFL (HR, 2.324; 95% CI, 1.372–3.939; $p = 0.002$), ICD without CRT implantation (HR, 2.377; 95% CI, 1.332–4.244; $p = 0.004$), and multiple zones (HR, 1.852; 95% CI, 1.163–2.951, $p = 0.010$) were identified

as risk factors for the first inappropriate ICD therapy event (Table 2).

The Kaplan-Meier curves indicated a significantly higher risk for the first inappropriate ICD therapy event in patients with AF/AFL than in those without AF/AFL at 12 months (14.4% vs. 5.9%, log-rank $p = 0.001$; Fig. 1B). The risk of the first inappropriate ICD therapy event was significantly higher in patients treated with an ICD than in those treated with CRT-D at 12 months (8.7% vs. 3.1%, log-rank $p < 0.001$; Fig. 1C).

3.4. Risk factors for the second inappropriate ICD therapy event

After the first inappropriate ICD therapy event, the following interventions were performed, including a change in the ICD programming ($n = 89$), initiation of or change in medication ($n = 23$)

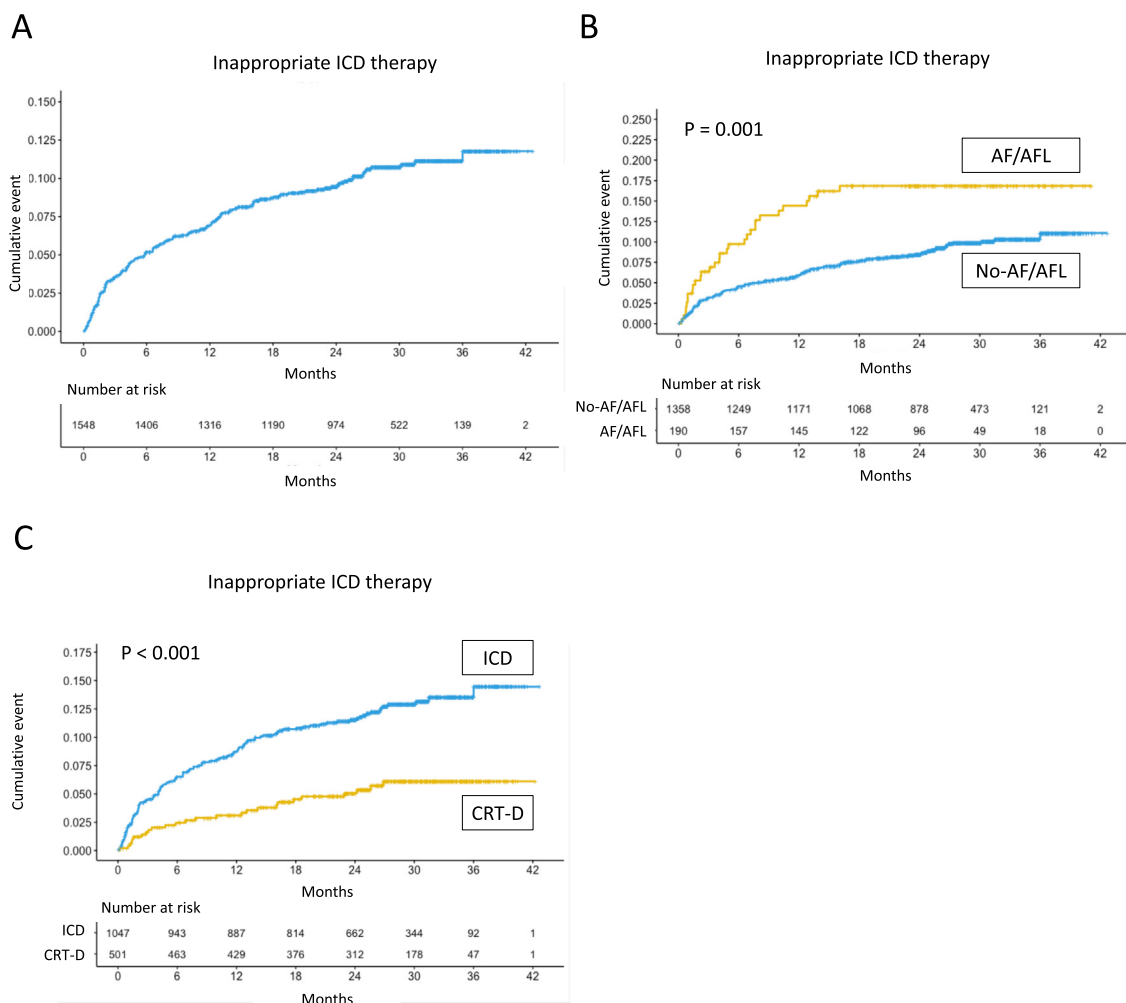


Fig. 1. Cumulative probability of (A) an inappropriate ICD therapy event; (B) an inappropriate ICD therapy among patients *with* and *without* atrial tachyarrhythmia prior to enrollment; and (C) an inappropriate ICD therapy among patients treated with ICD and CRT-D.

Table 2
Multivariate Cox regression analysis for the first inappropriate ICD therapy.

| | Inappropriate ICD therapy | |
|------------------------------------|---------------------------|-------|
| | HR (95% CI) | p |
| Age | 0.986 (0.973, 0.998) | 0.028 |
| Male | 0.779 (0.512, 1.187) | 0.246 |
| Atrial fibrillation/Atrial flutter | 2.324 (1.372, 3.939) | 0.002 |
| QRS duration | 0.994 (0.987, 1.000) | 0.060 |
| ICD | 2.377 (1.332, 4.244) | 0.004 |
| Without atrial lead | 0.932 (0.571, 1.520) | 0.779 |
| NYHA class, III/IV | 0.996 (0.589, 1.685) | 0.990 |
| Ejection fraction, % | 0.995 (0.983, 1.006) | 0.369 |
| Log BNP | 1.146 (0.818, 1.606) | 0.428 |
| Electrical storm | 0.750 (0.346, 1.625) | 0.466 |
| Secondary prevention | 0.957 (0.662, 1.385) | 0.817 |
| Multiple zones | 1.852 (1.163, 2.951) | 0.010 |

BNP denotes brain natriuretic peptide and was log 10 transformed.
ICD denotes implantable cardioverter defibrillator.

and catheter ablation (n = 4), or a combination of these interventions. Among the 89 ICD programming changes, 42 raised the detection zone of VT or VF, while the remaining 47 changes were precisely unknown. Precise medication change and catheter ablation data were also unavailable. The rate of the second inappropriate ICD therapy event after treatment for the first event was 37.6% at 12 months (Fig. 2A). The Kaplan-Meier curve indicated that the

rate of the second inappropriate ICD therapy event was lower among patients who received treatment after the first event than among those who did not (1.0% vs. 6.0% at one week, 4.2% vs. 22.3% at one month, 27.3% vs. 57.4% at one year, respectively, all log-rank p < 0.001; Fig. 2B). On multivariate Cox regression analysis, “no-intervention” after the first inappropriate ICD therapy event was retained as the sole risk factor for the second inappropriate ICD therapy event (HR, 3.521; 95% CI, 1.773–6.993; p = 0.001; Table 3).

4. Discussion

4.1. New findings

Our post-hoc secondary analysis identified younger age, ICD without CRT implantation, history of AF/AFL, and multiple zones as risk factors for the first inappropriate ICD therapy event. Treatment after the first inappropriate ICD therapy event, including initiation of (or change in) medication and change in ICD programming and ablation, lowered the risk of the second inappropriate ICD therapy event. The risk factor for the second inappropriate ICD therapy event was “no-intervention” after the first inappropriate ICD therapy event.

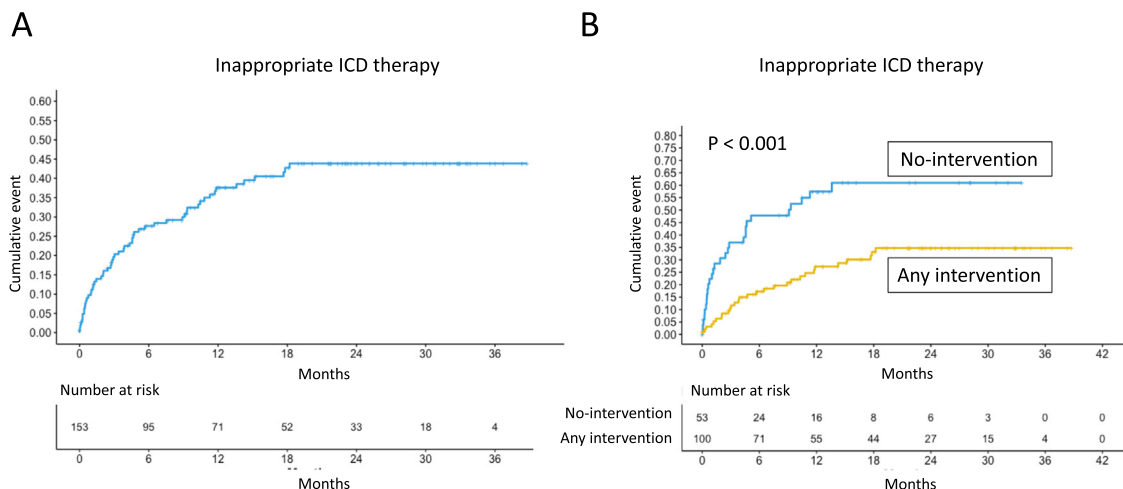


Fig. 2. Cumulative probability of the second event of inappropriate ICD therapy (A) after the first event of inappropriate ICD therapy among all patients and (B) among patients *with* or *without* treatment after the first event. An inappropriate ICD therapy includes both inappropriate anti-tachycardia pacing and shock.

Table 3
Multivariate Cox regression analysis for a second inappropriate ICD therapy.

| | Inappropriate ICD therapy | |
|---|---------------------------|-------|
| | HR (95% CI) | p |
| Age | 0.988 (0.965, 1.012) | 0.318 |
| Male | 1.716 (0.722, 4.078) | 0.222 |
| Atrial fibrillation/Atrial flutter | 1.547 (0.574, 4.168) | 0.389 |
| QRS duration | 1.000 (0.987, 1.014) | 0.980 |
| ICD | 2.088 (0.630, 6.919) | 0.229 |
| Without atrial lead | 0.856 (0.337, 2.173) | 0.744 |
| NYHA class, III/IV | 1.099 (0.419, 2.882) | 0.848 |
| Ejection fraction, % | 0.997 (0.977, 1.018) | 0.797 |
| Log BNP | 0.873 (0.512, 1.489) | 0.619 |
| Electrical storm | 0.642 (0.149, 2.776) | 0.554 |
| Secondary prevention | 1.739 (0.840, 3.600) | 0.136 |
| Multiple zones | 2.170 (0.793, 5.937) | 0.132 |
| No-intervention after the first inappropriate ICD therapy | 3.521 (1.773, 6.993) | 0.001 |

BNP denotes brain natriuretic peptide and was log 10 transformed. ICD denotes implantable cardioverter defibrillator.

4.2. Second inappropriate ICD therapy

Several therapeutic interventions after the first inappropriate ICD therapy event have been used, including a change in ICD programming, initiation of (or change in) medication, and catheter ablation [17]. Korte et al. [18] tried atrio-ventricular nodal catheter ablation, cavo-tricuspid isthmus ablation and pulmonary vein isolation in patients suffered from repetitive inappropriate ICD therapies. The inappropriate ICD therapy rate was significantly reduced after catheter ablation. Miyazaki et al. [19] reported the recurrent rate of inappropriate ICD therapy in 18 patients who received inappropriate ICD therapy due to atrial tachyarrhythmia and undertook

catheter ablation. During the median follow-up of 19.0 (9.5–37.3) months after the last procedure, no patients experienced any inappropriate shocks. A change in ICD programming or medication have been tried first after the first inappropriate ICD therapy. In our study, main interventions were also a change in ICD programming or initiation of (or change in) after inappropriate ICD therapy. Catheter ablation may be aggressively tried. Our study identified that treatment after the first inappropriate ICD therapy event lowered the risk for the second event. This is an important finding as more frequent events of inappropriate ICD therapy is associated with poor clinical outcomes and higher mortality rate [4,5]. As such, prevention of the second inappropriate ICD therapy event is as important as prevention of the first inappropriate ICD therapy event. Recently, remote monitoring has been shown to be useful for the prevention of inappropriate ICD therapy [20,21]. Although there is no information of remote monitoring in the present study, remote monitoring may also play a major role in detecting an inappropriate ICD therapy event, allowing for an appropriate treatment that could prevent a subsequent inappropriate ICD therapy event as early as possible [20].

4.3. ICD versus CRT-D

In a small retrospective cohort analysis of prospectively collected data, Chen et al. [11] reported a lower rate of inappropriate ICD shock for CRT-D than ICD treatment. Similarly, Kutyla et al. [12] reported a lower risk of inappropriate ICD therapy and shock among patients implanted with a CRT-D than among those implanted with an ICD (inappropriate therapy, 6% vs. 12%, respectively; shock, 2% vs. 5%, respectively). These findings were consistent with those of our study. The better outcomes for CRT-D may be due to an improvement in the functional capacity of CRT-D, compared to ICD, to induce reverse remodeling of the left atrium, which leads to a significant decrease in atrial tachy-arrhythmia [22–24]. Along with the result that a lower rate of inappropriate ICD shock for CRT-D than ICD, baseline QRS width and QT interval were significantly shorter in patients with inappropriate ICD therapy than those without (Table 1).

Conduction disturbance may be another reason for the lower inappropriate ICD therapy rate in patients with CRT-D than in those with ICD. During AF, a rapid ventricular response may not occur because of intrinsic conduction disturbance; consequently, inappropriate ICD therapy could be avoided.

4.4. Prior AF/AFL

Notably, atrial tachycardia and AF/AFL are the most frequent reasons for inappropriate ICD therapy. In the MADIT-II trial [5], inappropriate ICD shocks occurred in 83 out of 719 patients (11.5%). AF/AFL was the most common mechanism of inappropriate shock. A sub-analysis of the MADIT-RIT data [13] indicated that patients with a history of AF were at a higher risk for inappropriate ICD therapy (HR, 2.10; 95% CI, 1.38–3.20; $p < 0.001$) and inappropriate ICD shock (HR, 2.56; 95% CI, 1.38–4.74; $p = 0.003$) than patients without a prior history of AF. Recently, the stability criteria and morphological template have been available to avoid inappropriate ICD therapy due to AF/AFL. However, rapid ventricular response events could be particularly stable and likely conduct aberrantly, followed by inappropriate ICD therapy. In our study, AF/AFL was also identified as a risk factor for inappropriate ICD therapy. ICD programming should be optimized in all patients irrespective of a history of atrial tachyarrhythmia, not only in those currently known to have a higher risk of inappropriate ICD therapy.

4.5. Age

A sub analysis of the MADIT-RIT data [14] identified an inverse relationship between age and inappropriate ICD therapy. The cumulative Kaplan-Meier incidence curves revealed an inverse relationship between increasing quartiles of age (Q1: ≤ 55 , Q2: 56–64, Q3: 65–71, and Q4: ≥ 72 years) and inappropriate ICD therapy events. In agreement with our study, an inappropriate ICD therapy event was more likely to occur in younger than older patients. As previously reported [14], despite the higher frequency of atrial tachyarrhythmia among older patients, the attenuated ventricular response might offer some protection to older patients against inappropriate ICD therapy.

4.6. Single zone versus multiple zones

Single zone or multiple zones options are available in recent ICD models, allowing the application of different stimulation criteria to various locations of arrhythmias. Additionally, as some manufacturers also include supraventricular tachycardia discrimination algorithms, programming for more than one tachycardia zone allows for greater specificity in discriminating VT from supraventricular tachycardia. Although the effectiveness of single-zone and multiple-zone programming has not been specifically evaluated in a head-to-head comparison, in the MADIT-RIT study [9], the single-zone arm (high rate) was comparable to the triple-zone (delayed) arm with regard to inappropriate shock. In our present study, the rate of inappropriate ICD therapy was significantly higher for multiple zones than for a single zone. However, consistent with the findings of previous studies, there was no significant difference in the inappropriate ICD shock between these two groups (data not shown). Multiple zones had a lower cut-off rate than the single zone (155.4 vs. 193.3 bpm, $p < 0.001$), and patients treated using multiple zones were more likely to suffer from inappropriate ICD therapy. Actually, the minimum cut-off rate was significantly lower in patients who received inappropriate ICD therapy than in those who did not in this study. The cut-off rate for the lowest zone was relatively low as compared to that in the previous study. More than 50% of patients in this study were implanted ICR or CRT-D for secondary prevention. Class III antiarrhythmic drugs were used in more than 30% of patients, in whom the VT rate was likely to decrease. Therefore, these were the main reasons for the low cut-off heart rate.

4.7. Limitations

The limitations of our study need to be acknowledged in the interpretation of findings. First, our analysis is a post-hoc secondary analysis, which carries the bias inherent to this type of analysis. Second, there is no information in the Nippon Storm Study to discriminate AF from atrial tachycardia and AFL; therefore, precise analysis based on the type of atrial tachyarrhythmia was not possible. Third, clinical characteristics between patients in the ICD and CRT-D groups, as well as between the groups of patients *with* and *without* AF/AFL, were different, which may have influenced the predictors of inappropriate ICD therapy that we identified. Fourth, precise algorithms for discriminating supraventricular tachycardia, including morphological template, stability criteria, and sudden-onset data, were not available, making it impossible to analyze the effectiveness of each algorithm.

5. Conclusions

This is the first study to have focused on identifying predictive factors for the first and second inappropriate ICD therapy events. Risk factors for the first inappropriate ICD therapy event were similar to those previously reported. Immediate intervention after the first inappropriate ICD therapy event could reduce the likelihood of the second inappropriate ICD therapy event. Overall, our study provides information that can help to guide physicians in making decisions about the type of ICD treatment and the follow-up required.

Funding

No funding was received.

Declaration of Competing 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.

Acknowledgments

We gratefully acknowledge all 48 Japanese implantable cardioverter defibrillator device centers involved in this study, Japan Arrhythmia Device Industry Association, and the office of the Japanese Heart Rhythm Society, especially Ms. Yoko Sato, for data collection.

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

Department of Cardiology, Okinawa Prefectural Chubu Hospital

References

- [1] 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, I.I.I. Multicenter automatic defibrillator implantation trial, prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction, *N. Engl. J. Med.* 346 (12) (2002) 877–883.
- [2] 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 (21) (2004) 2140–2150.
- [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 (3) (2005) 225–237.
- [4] 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 (10) (2008) 1009–1017.
- [5] J.P. Daubert, W. Zareba, D.S. Cannom, S. McNitt, S.Z. Rosero, P. Wang, C. Schuger, J.S. Steinberg, S.L. Higgins, D.J. Wilber, H. Klein, M.L. Andrews, W.J. Hall, A.J. Moss, Inappropriate implantable cardioverter-defibrillator shocks in MADIT II: frequency, mechanisms, predictors, and survival impact, *J. Am. Coll. Cardiol.* 51 (14) (2008) 1357–1365.
- [6] A. Rahmawati, A. Chishaki, T. Ohkusa, H. Sawatari, M. Tsuchihashi-Makaya, Y. Ohtsuka, M. Nakai, M. Miyazono, N. Hashiguchi, H. Sakurada, M. Takemoto, Y. Mukai, S. Inoue, K. Sunagawa, H. Chishaki, Influence of primary and secondary prevention indications on anxiety about the implantable cardioverter-defibrillator, *J. Arrhythm.* 32 (2) (2016) 102–107.
- [7] S.F. Sears, L. Rosman, S. Sasaki, Y. Kondo, L.D. Sterns, E.J. Schloss, T. Kurita, A. Meijer, J. Rajmakers, B. Gerritse, A. Auricchio, Defibrillator shocks and their effect on objective and subjective patient outcomes: results of the PainFree SST clinical trial, *Heart Rhythm* 15 (5) (2018) 734–740.
- [8] B.L. Wilkoff, B.D. Williamson, R.S. Stern, S.L. Moore, F. Lu, S.W. Lee, U.M. Birgersdotter-Green, M.S. Wathen, I.C. Van Gelder, B.M. Heubner, M.L. Brown, K.K. Holloman, 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.* 52 (7) (2008) 541–550.
- [9] A.J. Moss, C. Schuger, C.A. Beck, M.W. Brown, D.S. Cannom, J.P. Daubert, N.A. Estes 3rd, H. Greenberg, W.J. Hall, D.T. Huang, J. Kautzner, H. Klein, S. McNitt, B. Olshansky, M. Shoda, D. Wilber, W. Zareba, Reduction in inappropriate therapy and mortality through ICD programming, *N. Engl. J. Med.* 367 (24) (2012) 2275–2283.
- [10] A. Auricchio, E.J. Schloss, T. Kurita, A. Meijer, B. Gerritse, S. Zweibel, F.M. AlSmaili, C.T. Leng, L.D. Sterns, 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* 12 (5) (2015) 926–936.
- [11] Z. Chen, T. Kotecha, S. Crichton, A. Shetty, M. Sohail, A. Arujuna, S. Kirubakaran, J. Bostock, M. Cooklin, M. O'Neill, M. Wright, J.S. Gill, C.A. Rinaldi, Lower incidence of inappropriate shock therapy in patients with combined cardiac resynchronization therapy defibrillators (CRT-D) compared with patients with non-CRT defibrillators (ICDs), *Int. J. Clin. Pract.* 67 (8) (2013) 733–739.
- [12] V. Kutyifa, J.P. Daubert, C. Schuger, I. Goldenberg, H. Klein, M.K. Aktas, S. McNitt, M. Stockburger, B. Merkely, W. Zareba, A.J. Moss, Novel ICD programming and inappropriate ICD therapy in CRT-D versus ICD patients: a MADIT-RIT sub-study, *Circ. Arrhythm. Electrophysiol.* 9 (1) (2016) e001965.
- [13] V. Kutyifa, A.J. Moss, C. Schuger, S. McNitt, B. Polonsky, A.H. Ruwald, M.H. Ruwald, J.P. Daubert, W. Zareba, Reduction in inappropriate ICD therapy in MADIT-RIT patients without history of atrial tachyarrhythmia, *J. Cardiovasc. Electrophysiol.* 26 (8) (2015) 879–884.
- [14] Y. Biton, D.T. Huang, I. Goldenberg, S. Rosero, A.J. Moss, V. Kutyifa, S. McNitt, B. Strasberg, W. Zareba, A. Barsheshet, Relationship between age and inappropriate implantable cardioverter-defibrillator therapy in MADIT-RIT (Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy), *Heart Rhythm* 13 (4) (2016) 888–893.
- [15] T. Noda, T. Kurita, T. Nitta, Y. Chiba, H. Furushima, N. Matsumoto, T. Toyoshima, A. Shimizu, H. Mitamura, K. Okumura, T. Ohe, Y. Aizawa, Significant impact of electrical storm on mortality in patients with structural heart disease and an implantable cardiac defibrillator, *Int. J. Cardiol.* 255 (2018) 85–91.
- [16] 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 (8) (2014) 1989–1991.

- [17] B.L. Wilkoff, L. Fauchier, M.K. Stiles, C.A. Morillo, S.M. Al-Khatib, J. Almendral, L. Aguinaga, R.D. Berger, A. Cuesta, J.P. Daubert, S. Dubner, K.A. Ellenbogen, N.A. Mark Estes 3rd, G. Fenelon, F.C. Garcia, M. Gasparini, D.E. Haines, J.S. Healey, J. L. Hurtwitz, R. Keegan, C. Kolb, K.H. Kuck, G. Marinskis, M. Martinelli, M. McGuire, L.G. Molina, K. Okumura, A. Proclemer, A.M. Russo, J.P. Singh, C.D. Swerdlow, W.S. Teo, W. Uribe, S. Viskin, C.C. Wang, S. Zhang, 2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing, *Heart Rhythm* 13 (2) (2016) e50–e86.
- [18] T. Korte, M. Niehaus, O. Meyer, J. Tebbenjohanns, Prospective evaluation of catheter ablation in patients with implantable cardioverter defibrillators and multiple inappropriate ICD therapies due to atrial fibrillation and type I atrial flutter, *Pacing Clin. Electrophysiol.* 24 (7) (2001) 1061–1066.
- [19] S. Miyazaki, H. Taniguchi, S. Kusa, Y. Komatsu, N. Ichihara, T. Takagi, J. Iwasawa, A. Kuroi, H. Nakamura, H. Hachiya, K. Hirao, Y. Iesaka, Catheter ablation of atrial tachyarrhythmias causing inappropriate implantable cardioverter-defibrillator shocks, *Europace* 17 (2) (2015) 289–294.
- [20] L. Guedon-Moreau, D. Lacroix, N. Sadoul, J. Clementy, C. Kouakam, J.S. Hermida, E. Aliot, M. Boursier, O. Bizeau, S. Kacet, A randomized study of remote follow-up of implantable cardioverter defibrillators: safety and efficacy report of the ECOST trial, *Eur. Heart J.* 34 (8) (2013) 605–614.
- [21] N. Nishii, A. Miyoshi, M. Kubo, M. Miyamoto, Y. Morimoto, S. Kawada, K. Nakagawa, A. Watanabe, K. Nakamura, H. Morita, H. Ito, Analysis of arrhythmic events is useful to detect lead failure earlier in patients followed by remote monitoring, *J. Cardiovasc. Electrophysiol.* 29 (3) (2018) 463–470.
- [22] A. Brenyo, M.S. Link, A. Barsheshet, A.J. Moss, W. Zareba, P.J. Wang, S. McNitt, D. Huang, E. Foster, M. Estes 3rd, S.D. Solomon, I. Goldenberg, Cardiac resynchronization therapy reduces left atrial volume and the risk of atrial tachyarrhythmias in MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy), *J. Am. Coll. Cardiol.* 58 (16) (2011) 1682–1689.
- [23] S.D. Solomon, E. Foster, M. Bourgoun, A. Shah, E. Vioria, M.W. Brown, W.J. Hall, M.A. Pfeffer, A.J. Moss, Effect of cardiac resynchronization therapy on reverse remodeling and relation to outcome: multicenter automatic defibrillator implantation trial: cardiac resynchronization therapy, *Circulation* 122 (10) (2010) 985–992.
- [24] C.M. Yu, F. Fang, Q. Zhang, G.W. Yip, C.M. Li, J.Y. Chan, L. Wu, J.W. Fung, Improvement of atrial function and atrial reverse remodeling after cardiac resynchronization therapy for heart failure, *J. Am. Coll. Cardiol.* 50 (8) (2007) 778–785.