RESEARCH

Clinical impact of applying strategic programming in patients with implantable cardioverter-defibrillators beyond reducing inappropriate shocks

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Abstract

Background: The incidence of inappropriate shocks remains high at 30% in patients with implantable cardioverter-defibrillators (ICDs). This retrospective study sought to examine the efficacy of strategic programming (ICD programming with a long detection interval and high-rate cutoff) in reducing electrical storm, inappropriate shocks, and unexpected hospital visits in patients with ICDs with/without cardiac resynchronization therapy with defibrillator (CRT-Ds).

Methods: This was a single tertiary center retrospective study, evaluating the clinical outcomes, especially regarding inappropriate therapies in patients with ICDs or CRT-Ds. Enrolled patients underwent ICD or CRT-D implantations from January 2008 to May 2016. Clinical information was attained by a thorough chart review.

Results: We analyzed 155 defibrillator patients from January 2008 to May 2016 (124 patients had ICDs and 31 had CRT-Ds). Since we adopted this strategic programming as a default programming from 2015 implanted ICDs and CRT-Ds, we divided the patients into two groups: devices implanted before 2015 (group A, $n = 94$) versus implanted after 2015 (group B, $n = 61$). During a median of 1289 days of follow-up, electrical storms occurred in three patients (eight events) in group B versus 11 (28 events) in group A ($P = 0.18$); appropriate therapies were delivered in 27 patients (56 events) in group A versus 7 (15 events) in group B ($P = 0.72$); inappropriate therapies were delivered in 15 patients (21 events) in group A versus 1 with 1 episode in group B ($P = 0.03$); and 5 unexpected hospitalizations occurred in four patients in group B versus 36 in 24 patients in group A ($P = 0.02$).

Conclusion: The clinical application of strategic programming reduced inappropriate shocks and unexpected hospitalizations in ICD and CRT-D patients.

Keywords: Defibrillators, Implantable, Cardiac resynchronization therapy devices, Tachycardia, Ventricular, Ventricular fibrillation

Introduction

Currently, many algorithms are provided in modern ICDs to enhance the automatic detection of ventricular arrhythmias [1–5]; however, there are yet many pitfalls, and programming of the ICDs still affects the patient outcomes [6–8]. According to previous studies, any ventricular therapy is related to a worse long-term outcome regarding the mortality and a decreased quality of life with psychological problems [9–11]. In the ADVANCE

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III [12] trial, a long detection interval with anti-tachycardia pacing (ATP) was feasible for ICDs for both primary and secondary prevention. MADIT-RIT [11] also implied a high-rate cutoff or prolonged detection of ventricular arrhythmias reduces inappropriate ICD shocks. In the PROVE trial [13], investigators demonstrated strategic programming with a chosen rate cutoff and the detection interval was also safe and effective for primary prevention patients. Based on these results, we applied strategic programming protocols since January 2015. We sought to evaluate the effectiveness of strategic programming (ICD programming with a long detection interval) in reducing electrical storms, inappropriate shocks, and unexpected hospital visits in patients with ICDs with/without resynchronization therapy with defibrillator (CRT-Ds).

Materials and methods

Patients

This is a single tertiary center retrospective study, evaluating the clinical outcomes, especially regarding inappropriate therapies and hospitalizations in patients with ICDs or CRT-Ds. We identified 160 patients who underwent an ICD or CRT-D implantation from January 2008 to May 2016 and excluded five patients due to follow-up loss and a lack of follow-up data, resulting in a total of 155 patients included in the study. For a comparison, we divided the patients into two groups: An ICD or CRT-D implanted before the year 2015 in which conventional ICD programming was applied (Group A, $n = 94$) versus that implanted after 2015 in which strategic programming with a long detection interval and higher rate cutoff was applied (Group B, $n = 61$).

Main difference after applying strategic programming was adopting monitoring without therapy in 165–180 beats per minute (BPM) zone in group B compared to group A. Also after strategic programming, default detection was prolonged to 30(or 24) out of 40(or 36) beats from 12 out of 24 beats in 181–200 BPM zone. This study was approved by the Institutional Review Board of Asan Medical Center (Seoul, South Korea; Institutional Review Board No. 2018-2261-0001).

Clinical parameters

The patient-related data included baseline characteristics such as the age and sex. Clinical characteristics including a history of arrhythmic events relating to sudden cardiac death (SCD), types of documented arrhythmias, underlying structural heart diseases, NYHA class, and a past medical history of hypertension, coronary artery disease, chronic kidney disease, and atrial fibrillation. In addition, the device-related parameters (type of the device, programming parameters, implanted and programmed dates, degree of prevention, and device-related

complications) were gathered. Finally, follow-up information including the follow-up duration, occurrence of cardiac death or a heart transplantation, and whether appropriate/inappropriate therapy deliveries were given or not was reviewed. Reprogramming information, along with the changes in medications following events, was thoroughly reviewed.

Evaluation of ICD therapies and follow-up

The primary end point of this study was the number of inappropriate shock and hospitalization events before and after applying a long detection interval and higher rate cutoff for ventricular arrhythmias.

The definition of an inappropriate therapy was defined as any ICD therapy delivered when no VT (ventricular tachycardia) or VF (ventricular fibrillation) existed. The definition of appropriate shocks or therapies was defined as any ICD therapy delivered for VT or VF. All therapies were subdivided into ATP or shocks. If both ATP and a shock were delivered in a single episode, it was categorized into a shock episode. For the results, only the number of shock therapies was used for the inappropriate therapy analysis. Electrical storm(ES) events were defined by 3 or more sustained episodes of ventricular tachycardia, ventricular fibrillation, or appropriate shocks from an implantable cardioverter-defibrillator within 24 h. Investigators checked every implanted device on schedule. The interrogation schedule was as follows: on the day of the implantation, the day after the implantation, 1 month after the implantation, and every 3–6 months thereafter. If the patient had received an ICD therapy or was hospitalized for any reason, we performed the device interrogation on demand. During the interrogation of the device, the investigators reviewed whether a therapy was given or not, and if a therapy history existed, the stored EGMs were reviewed to determine their appropriateness.

Statistical analysis

Continuous variables were examined with the *t* test when appropriate and were expressed as the mean ± standard deviation. Continuous variables that were not normally distributed were described as the median ± interquartile range using a Mann–Whitney *U* test. We described the categorical variables using frequencies and compared them using a chi-square test or Fisher exact test as appropriate. To investigate the difference in the incidence rate of each outcome between Groups A and B, we used a negative binomial regression model, which is appropriate for count data with excessive zeros. To account for the different lengths of follow-up for the different patients, a log of the follow-up duration was included in the model as an offset term. To handle any slight overdispersion, we used a robust estimator of the standard error to calculate

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the 95% confident intervals and p-values. In the univariate analysis, we investigated the association between each candidate factor and the outcome. The factors that were statistically significant in the univariate analysis or that were deemed clinically important were entered into the multivariable analysis. The final multivariate model was determined by a backward elimination. There were no missing values in any of the factors or outcomes in the analysis. The statistical analyses were performed using R 3.5.1 statistical software (R Foundation for Statistical Computing, Vienna, Austria, 2018).

Results
Patient characteristics
Overall, the mean age of the patients was 54.2 ± 15 years, and the devices were implanted for primary prevention in 50 patients (32.3%) and secondary prevention in 105 (67.7%). An ICD was implanted in 123 patients (79.4%), and 32 had a CRT-D (20.6%). Ninety-four patients were implanted with an ICD or CRT-D before 2015 (group A), and 61 were implanted after 2015 (group B). The baseline characteristics of the patients and devices are described in Tables 1 and 2. The mean follow-up after the device implantation was 1629.1 ± 678.2 days versus 981.4 ± 318.6 days, for groups A and B, respectively.

Appropriate and inappropriate therapies
During the follow-up, overall, appropriate therapies were delivered in 34 patients (71 episodes) and inappropriate therapies in 16 (22 episodes). An inappropriate therapy was delivered in 15 patients (21 events) in group A versus 1 patient with 1 episode in group B ($P = 0.03$). After applying a long detection interval in the ICD programming in group A, there were no inappropriate therapies or clinical events related to a delayed ventricular arrhythmia detection. Appropriate therapies occurred in 27 patients (56 shocks and 14 ATP terminated events) in group A and 7 (15 shocks, ATP terminated events were 5) in group B ($P = 0.72$). Regarding the ESs in group A, there were 24 events in 11 patients before strategic programming, while there were four events in three patients after strategic ICD programming (all three of them had a previous ES history). In group B, three patients experienced a total of

Table 1 Baseline characteristics of the patients and implanted devices

	Group A (*n* = 94)	Group B (*n* = 61)	*P* value
Age (year)	52.9 ± 15.5	56.3 ± 14.1	0.16
Sex			
Male (%)	75 (79.8)	52 (85.2)	0.52
Degree of prevention (%)			0.77
Primary prevention	29 (30.9)	21 (34.4)	
Secondary prevention	65 (69.1)	40 (65.6)	
Type of arrhythmia (%)			0.75
Ventricular tachycardia	35 (37.2)	20 (32.8)	
Ventricular fibrillation	36 (38.3)	23 (37.7)	
Type of device (no. of secondary prevention)			0.11
Single-chamber ICD	31 (24)	22 (19)	
Dual-chamber ICD	48 (38)	22 (18)	
CRT-D	15 (3)	17 (3)	
Underlying cardiac disease (no. of patients)			0.21
Structurally normal	45 (47.9)	24 (39.3)	
Structurally abnormal but normal LV systolic function	19 (20.2)	9 (14.8)	
Structurally abnormal and reduced LV systolic function	30 (31.9)	28 (45.9)	
NYHA class (%)			0.26
NYHA I	49 (52.1)	24 (39.3)	
NYHA II	28 (29.8)	21 (34.4)	
NYHA III/IV	17 (18.1)	16 (26.2)	
Hypertension (%)	46 (48.9)	30 (49.2)	1
Diabetes mellitus (%)	16 (17.0)	16 (26.2)	0.24
Chronic kidney disease (%)	5 (5.3)	12 (19.7)	0.01
Cerebrovascular attack (%)	9 (9.6)	7 (11.5)	0.91

ICD implantable cardiac defibrillator, *CRT-D* cardiac resynchronization therapy-defibrillator

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Table 2 Underlying cardiac conditions and underlying heart diseases

	Group A	Group B
Structurally normal	45	24
Brugada syndrome	7	5
Idiopathic VF	32	19
Long QT syndrome	5	1
Variant angina	1	0
Structurally abnormal but normal LV systolic function		
Amyloidosis	2	0
ARVC	6	1
Myotonic dystrophy	0	1
Sarcoidosis	1	1
HCMP	10	6
Structurally abnormal and reduced LV systolic function		
DCMP	20	16
ICMP	10	12

ARVC arrhythmogenic right ventricular cardiomyopathy, *DCMP* dilated cardiomyopathy, *HCMP* hypertrophic cardiomyopathy, *ICMP* ischemic cardiomyopathy, *VF* ventricular fibrillation

eight ES events ($P = 0.18$). All ES events were included in the appropriate therapy. All of the ES events led to an unexpected hospitalization, and some of the ES events took place during the hospitalization.

Events with ICDs versus CRT-Ds

There were seven appropriate therapeutic events in three patients with CRT-Ds (five ATPs in three patients and two shock events in a single patient with secondary prevention). Among them, two patients were implanted for secondary prevention. There was no inappropriate therapy in the CRT-D-implanted patients. However, only 32 CRT-D-implanted patients were included in the present study; however, it is noteworthy that much fewer inappropriate therapies occurred in the CRT-D patients (Fig. 1).

Hospital visits

Unexpected patient hospitalizations or outpatient clinic visits due to any ICD therapy were far less after applying the strategic programming. The number of hospitalizations was five in four patients in group B, while there were 36 hospitalizations in 24 patients in group A ($P = 0.02$) (Fig. 2).

Mortality and major cardio-cerebrovascular events

During the follow-up, eight patients died of a heart failure aggravation and one of them underwent radiofrequency catheter ablation for numerous VT storms with recurrent shocks and died of a heart failure aggravation. Four patients underwent radiofrequency catheter ablation for ventricular arrhythmias. Five patients underwent a heart transplantation. The predicting factors of mortality were any hospitalization event (HR 3.39 [1.2–9.6]; $P = 0.02$, Fig. 3a) and a higher NYHA classification by a multivariate analysis (HR 2.2 [1.2–3.9], $P = 0.008$, Fig. 3b).

Discussion

There is much evidence that a prolonged detection time with anti-tachycardia pacing effectively reduces inappropriate shocks in ICD/CRT-D-implanted patients. Even considering the heterogeneity of underlying cardiac conditions, these methods of programming have been effective and safe in secondary prevention patients [14, 15].

In the present study, we demonstrate a definite reduction in hospitalizations, not to mention a reduction in inappropriate therapies without any adverse events, when strategic ICD programming protocols were applied to the real-world clinical practice. The main cause of reducing hospitalizations is the significant reduction in inappropriate shocks after applying the strategic ICD program. A reduction in ES events was not observed in our study, but there was a reduction in ESs and related hospitalization benefits in the OBSERVO-ICD study [16]. In the OBSERVO-ICD study, a lower VF zone setting and inadequate ATPs or without a long detection interval were all independently related to increased ES events.

Before applying the strategic programming (a higher rate cutoff and long detection interval), there were more alterations following episodes of inappropriate therapies, such as modifications in the ICD programming including the tachycardia therapy zone, changing medications, which led to an increment in hospitalizations or unnecessary hospital visit events, and increased medical care costs. After applying the strategic ICD programming, the inappropriate ICD therapies dramatically decreased. Therefore, unexpected patient hospitalizations due to inappropriate therapies have decreased by 84% after the strategic programming in our study population. The decrease in the hospitalizations and hospital visits is directly related to a reduction in the medical cost expenditure.

In some patients with ICDs/CRT-Ds for primary prevention, the mortality benefit of the ICDs/CRT-Ds is undeniable [13, 17–19]. Especially, when comparing ICDs and CRT-Ds, CRT-D-implanted patients had fewer events than ICD-implanted patients, owing to an increased sensitivity in detecting supraventricular tachycardias and improved heart failure in CRT-D patients [8]. This was also consistent with our study population. As in

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Fig. 1 The total number of inappropriate shock events was lower in group B than group A
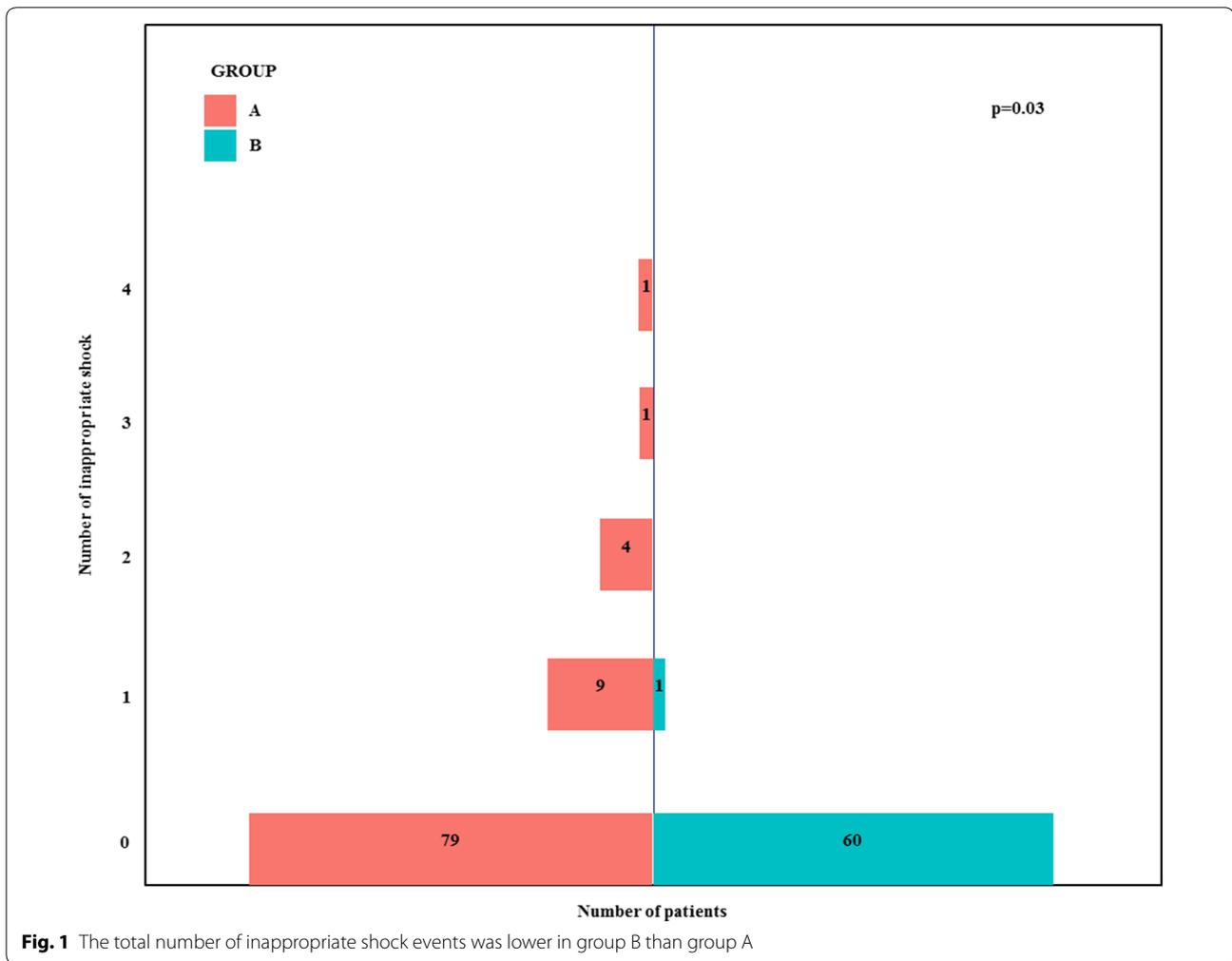
the fore-mentioned study, strategic programming of the devices in our patients also played a role in reducing the inappropriate shock deliveries.

In the previous studies [11–13], idiopathic VF, BS, and ERS patients were not included in the final analysis. In our study, those patients were also included as structurally normal heart patients. There were 69 patients without structural heart disease (12 patients had Brugada syndrome and 51 had idiopathic VF). There were two episodes of inappropriate therapies (shocks during AT) in one of the idiopathic VF patients before applying the long detection interval. After applying the long detection interval, there have been no inappropriate therapies in either group. By incorporating a long detection time, the discrimination between supraventricular arrhythmias and ventricular arrhythmias improves. In addition, when

programming devices in these patients without structural heart disease, the tachyarrhythmia therapy zone setting should differ from that in patients with structural heart disease [20]. That is because, usually those patients are younger with a higher exercise capacity and higher target heart rate.

Limitations

After applying the strategic programming, there were no further inappropriate therapies. Though programming a long detection interval seems feasible and safe, there is a limitation. It was difficult to compare the two groups divided by the timing of the implantation and application of the strategical programming, since the two groups were composed of heterogeneous-underlying cardiac disorders with variable follow-up durations. This study was designed to compare the clinical efficacy and safety,

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Fig. 2 The hospitalization events for groups A and B
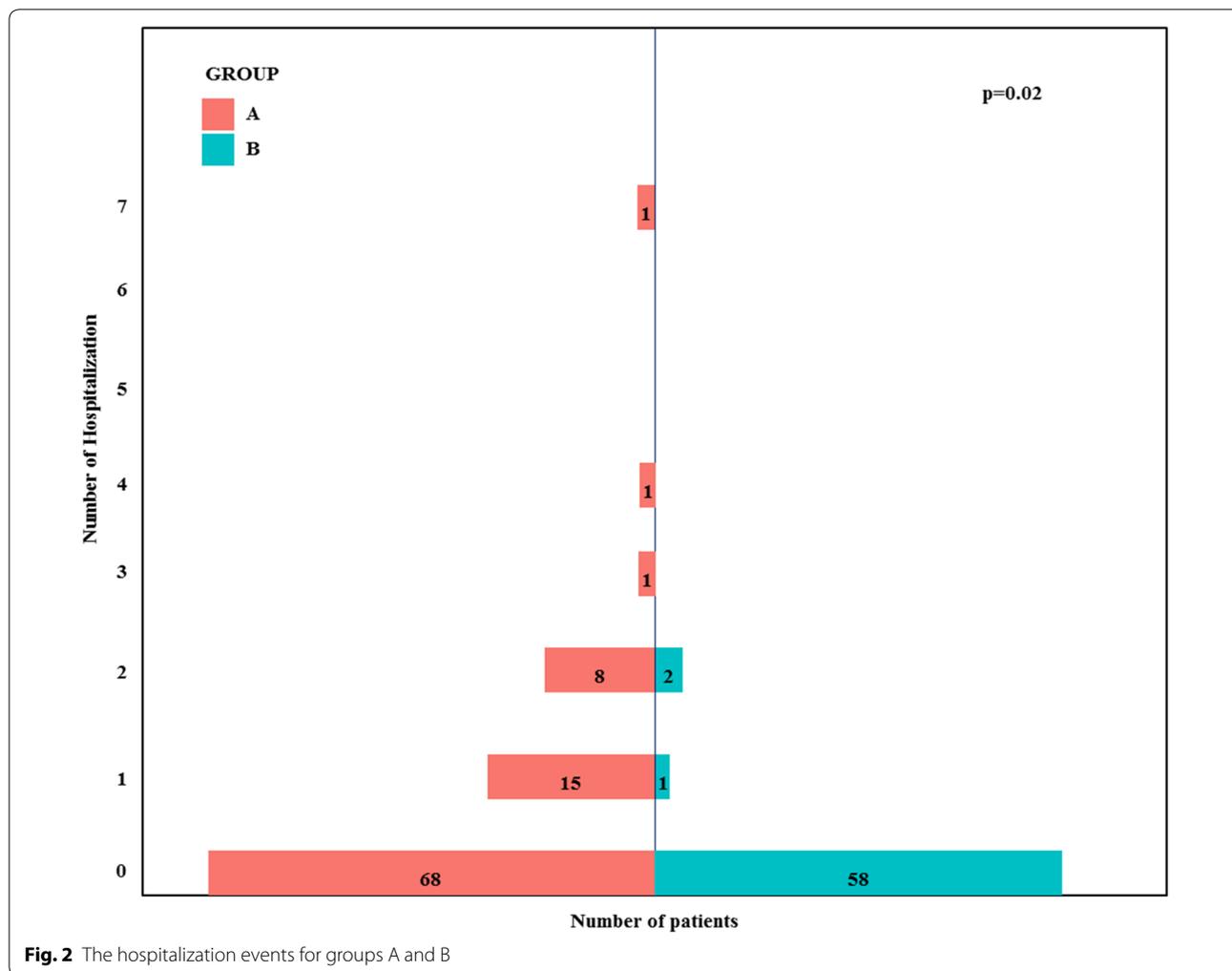
especially in terms of reducing inappropriate shocks and hospitalizations after the strategic programming application. In our study, even though the number of patients in the two groups differed notably, the number of inappropriate shocks and hospitalizations was significantly lower after the application of the fore-mentioned strategic programming. Although considering that the clinical course may vary among underlying cardiac diseases, after changing the ICD programming protocols from 2015 in group A, the overall hospitalization and inappropriate therapy event incidence rates markedly decreased without any adverse events.

Conclusion
The clinical application of a long detection interval and higher rate cutoff for the therapy in ICDs and CRT-Ds according to the ADVANCE III, MADIT-RIT, and PROVE trials showed a markedly lower incidence of hospital visits, not to mention reducing inappropriate therapies in both primary and secondary prevention patients without any complications. Strategic ICD programming is beneficial in terms of reducing hospitalizations, which decreases the medical cost and inappropriate shocks and results in a better prognosis.

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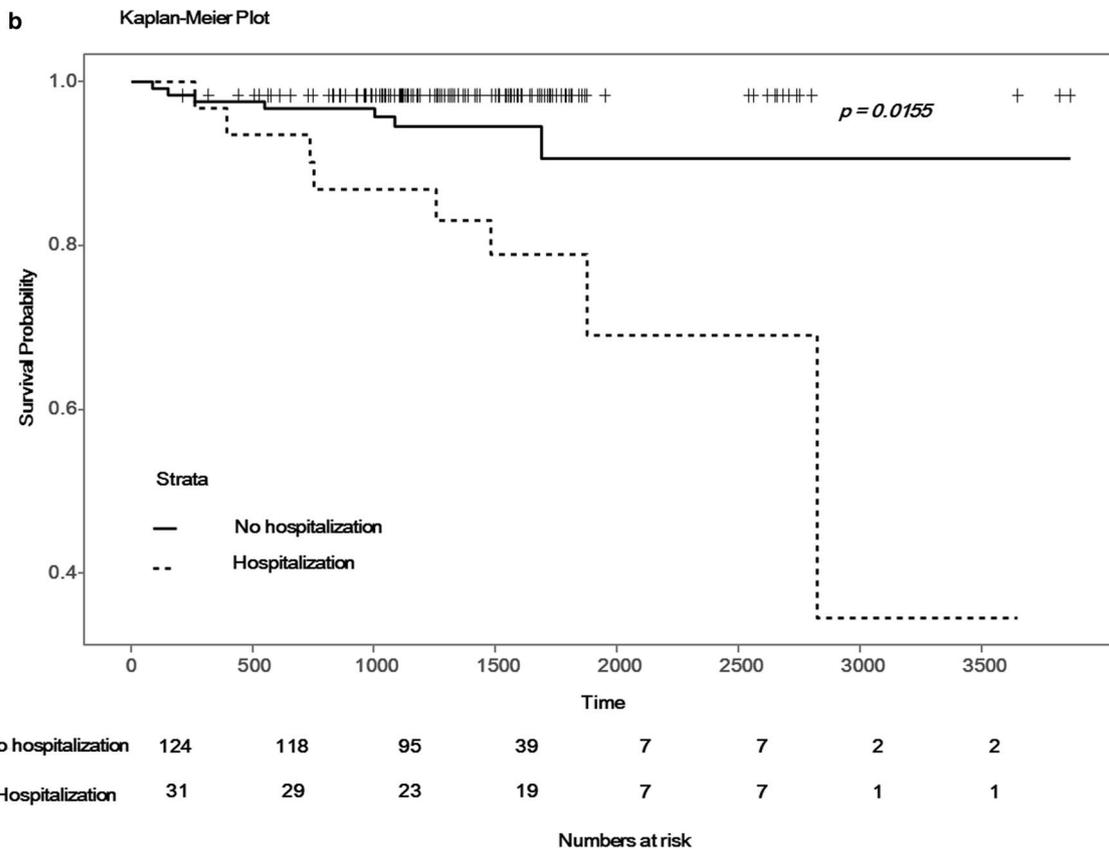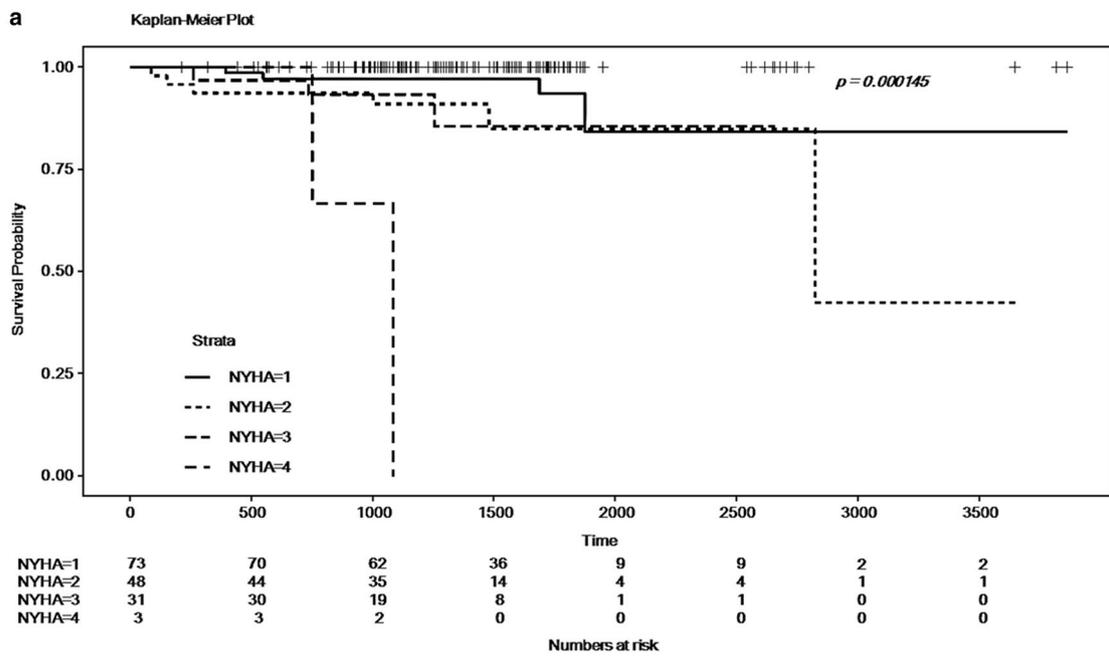
Fig. 3 Predictors of mortality in the present study population. **a** NYHA class III/IV patients have a higher mortality. **b** Patients with history of a hospitalization have a higher mortality

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Abbreviations
ICD: Implantable cardioverter-defibrillator; CRT-D: Cardiac resynchronization therapy with defibrillator; ATP: Anti-tachycardia pacing; VT: Ventricular tachycardia; VF: Ventricular fibrillation; SCD: Sudden cardiac death; ES: Electrical storms; BPM: Beats per minute.

Authors' contributions
YH analyzed and interpreted the patient data and a major contributor in writing the manuscript. GN, KC, and YK supervised the interpretation of the data and the manuscript. JK analyzed and made a final decision on the manuscript. SP analyzed the patient data and performed major statistical analysis. All authors read and approved the final manuscript.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
This study was approved by the Institutional Review Board of Asan Medical Center (Seoul, South Korea; Institutional Review Board No. 2018-2261-0001).

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

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