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Clinical Implications of Device-Detected Atrial Fibrillation in Cardiac Resynchronization Therapy

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AUTHOR'S SUMMARY

Effective biventricular (BiV) pacing is a determinant of cardiac resynchronization therapy (CRT) success, but atrial fibrillation (AF) can interfere with adequate BiV pacing and affect clinical outcomes. Device-detected AF during the follow-up period can occur in sinus rhythm patients at pre-implantation and affect the benefits of CRT. An important contribution of our study was that device-detected AF was associated with lower optimal BiV pacing (≥98%) and worse clinical outcomes including heart failure hospitalization, cardiovascular death, and all-cause death than no-AF. There were no significant differences in the optimal BiV pacing and clinical outcomes between the device-detected AF and the previous AF groups.

ABSTRACT

Background and Objectives: Atrial fibrillation (AF) is associated with decreased cardiac resynchronization therapy (CRT) benefits compared to sinus rhythm (SR). Effective biventricular (BiV) pacing is a determinant of CRT success, but AF can interfere with adequate BiV pacing and affect clinical outcomes. We investigated the effect of device-detected AF on clinical outcomes and optimal BiV pacing in patients with heart failure (HF) treated with CRT.
Methods: We retrospectively analyzed 174 patients who underwent CRT implantation between 2012 and 2019 at a tertiary center. The optimal BiV pacing percentage was defined as ≥98%. Device-detected AF was defined as an atrial high-rate episode ≥180 beats per minute lasting more than 6 minutes during the follow-up period. We stratified the patients without preexisting AF at pre-implantation into device-detected AF and no-AF groups.
Results: A total of 120 patients did not show preexisting AF at pre-implantation, and 54 had AF. Among these 120 patients, 19 (15.8%) showed device-detected AF during a median follow-up of 25.1 months. The proportion of optimal BiV pacing was significantly lower in the device-detected AF group than in the no-AF group (42.1% vs. 75.2%, p=0.009). The device-detected AF group had a higher incidence of HF hospitalization, cardiovascular death, and all-cause death than the no-AF group. The device-detected AF and previous AF groups showed no significant differences regarding the percentage of BiV pacing and clinical outcomes.

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Conflict of Interest
The authors have no financial conflicts of interest.

Data Sharing Statement
The data generated in this study is available from the corresponding author upon reasonable request.

Author Contributions
Conceptualization: Yoon M, Oh J, Kang SM; Data curation: Yoon M, Oh J, Chun KH, Yu HT, Lee CJ, Kim TH, Pak HN, Lee MH, Joung B, Kang SM; Formal analysis: Yoon M, Oh J, Kang SM; Funding acquisition: Kang SM; Investigation: Yoon M, Oh J, Chun KH, Yu HT, Lee CJ, Kim TH, Pak HN, Lee MH, Joung B, Kang SM; Methodology: Yoon M, Oh J, Chun KH, Kang SM; Project administration: Yoon M, Oh J, Kang SM; Resources: Yoon M, Oh J, Chun KH, Kang SM; Software: Yoon M, Oh J, Kang SM; Supervision: Yoon M, Oh J, Kang SM; Validation: Yoon M, Oh J, Kang SM; Visualization: Yoon M, Oh J, Kang SM; Writing - original draft: Yoon M, Oh J; Writing - review & editing: Yoon M, Oh J, Chun KH, Yu HT, Lee CJ, Kim TH, Pak HN, Lee MH, Joung B, Kang SM.

Conclusions: For HF patients implanted with CRT, device-detected AF was associated with lower optimal BiV pacing and worse clinical outcomes than no-AF.

Keywords: Cardiac resynchronization therapy; Atrial fibrillation; Heart failure

INTRODUCTION

Cardiac resynchronization therapy (CRT) is an approved therapeutic option for patients with heart failure (HF) with reduced ejection fraction and left ventricular (LV) dyssynchrony in current guidelines.[1)2)] It is associated with improved LV ejection fractions (LVEFs) and decreased morbidity and mortality[3)]; however, atrial fibrillation (AF) is associated with reduced CRT benefits compared to sinus rhythm (SR).[4)5)] The irregularity and rapid ventricular rate of AF may interfere with adequate biventricular (BiV) pacing delivery of CRT.[6)] Because effective BiV pacing is a determinant of CRT success,[7-9)] CRT is not as effective for AF patients as it is for SR patients.

Because AF is the most common arrhythmia in HF patients, the optimal management of AF, including rate or rhythm control, is critical for HF patients implanted with CRT.[1)2)] Also, AF burden or device-detected AF during the follow-up period after CRT implantation has recently received attention. An increased AF burden is associated with increased HF morbidities in CRT patients.[10)] Device-detected AF during the follow-up period can occur in SR patients at pre-implantation and affect the benefits of CRT.[11-13)] Therefore, it is important to assess device-detected AF in CRT patients during follow-up.

Only a few studies have evaluated the clinical consequences of device-detected AF in HF patients treated with CRT. However, whether device-detected AF is associated with a lower percentage of BiV pacing and poor clinical outcomes for CRT patients remains unclear. In the present study, we investigated the effect of device-detected AF on clinical outcomes and optimal BiV pacing in HF patients who underwent CRT implantation.

METHODS

Ethical statement

This study was approved by the Institutional Review Board of the Yonsei University Health System (1–2013-0061) and conducted in accordance with the Declaration of Helsinki (2013). Informed consent was obtained from all the patients.

Study population

We retrospectively analyzed 195 patients who underwent CRT implantation between September 2012 and September 2019 at a single tertiary university hospital. The CRT implantations were performed according to the guidelines for HF management (LVEF ≤35%, QRS duration ≥130 ms, and New York Heart Association (NYHA) functional class II, III despite optimal medical therapy for ≥3 months).[2)] We excluded 21 patients who were lost to follow-up within 6 months after the CRT implantation, or for whom the device was removed within 6 months. Finally, 174 patients were enrolled in this study.

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Device implantation and programming

All CRT devices were implanted transvenously using aseptic techniques. Conventional right ventricular and atrial leads were positioned in the right ventricular apex and right atrial appendage, respectively. The preferred sites for the LV lead implantation were the lateral or posterolateral cardiac veins through the coronary sinus. For patients who needed an implantable defibrillator, the defibrillation leads were positioned in the right ventricular apex. All the leads were connected to a dual chamber CRT device (VIVA, Consulta, or Amplia MRI QUAD; Medtronic Inc., Minneapolis, MN, USA; Unify, Quadra, Quadra Assura MP, or Quadra Allure MP; Abbott, St. Paul, MN, USA).

At implantation, the CRT was optimized based on the intracardiac electrogram from the leads. The CRT devices were programmed in the DDD (R) mode for the patients without preexisting AF or paroxysmal AF. The automatic mode switch was enabled to switch the pacing mode to a non-atrial tracking mode during AF or atrial tachycardia. Patients with persistent or permanent AF were programmed in VVIR mode. After CRT implantation, the patients were followed up at the clinic every 3 months. CRT interrogation and optimization based on the intracardiac electrograms was performed at every visit to achieve the optimal BiV pacing percentage based on the manufacturers' instructions and physician's discretion. The average BiV pacing percentage, which was obtained from the last available interrogation, was calculated as the average LV pacing percentage throughout the follow-up period, similar to previous study.[9] The optimal BiV pacing percentage was defined as ≥98%.[7][9][14]

Echocardiographic parameters

Transthoracic echocardiography was performed before and at 3, 6, and 12 months after CRT implantations. The LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) were measured from the apical 2- and 4-chamber views using the biplane disc method. The LVEF was calculated as: (LVEDV−LVESV)×100/LVEDV. The CRT response was defined as a decrease in the LVESV ≥15% on echocardiography at 6 or 12 months after the CRT implantation.[15-17] Valvular heart disease was defined as severe stenosis or regurgitation, or a history of previous valve surgery or intervention.

Device-detected atrial fibrillation and atrioventricular nodal ablation

The patients were stratified according to their rhythms at the time of CRT pre-implantation using 12-lead electrocardiogram (ECG) or 24-hour Holter monitoring. Patients with any type of AF, including paroxysmal, persistent, or permanent, were classified into a previous AF group. We stratified the patients without pre-existing AF at pre-implantation according to whether AF was detected by the device during the follow-up period. Device-detected AF was defined as an atrial high-rate episode ≥180 beats per minute lasting more than 6 minutes by cardiac implantable electronic devices according to current guideline position paper.[18][19]

For patients with AF, rate-slowing drugs (e.g., beta-blockers) were administered before CRT implantation and up-titrated after implantation to obtain an adequate rate control and maximal BiV pacing delivery. If an adequate BiV pacing percentage was not maintained with rate-slowing drugs, atrioventricular nodal ablation (AVNA) was considered within one month after the CRT implantation by physicians' discretion.

Clinical outcomes and follow-up

Guideline-directed medical treatment was administered during the follow-up period. The clinical endpoints were HF hospitalization, cardiovascular death, all-cause death, and

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appropriate implantable cardioverter-defibrillator (ICD) therapy. Appropriate ICD therapy was defined as anti-tachycardia pacing or shock therapy for ventricular tachyarrhythmia.

Statistical analysis

Descriptive statistics were used to characterize baseline characteristics and comorbidities. Categorical variables are reported as frequencies (percentages). Continuous variables are expressed as the mean ± standard deviation or medians with interquartile ranges. The categorical variables were compared using Fisher's exact test or the Pearson χ^2 test, and continuous variables were compared using Student's t-test or the Mann-Whitney U test. Survival analyses were performed using the Kaplan-Meier method, and the log-rank test was used to evaluate the differences between the survival trends.

All tests were two-tailed, and p value <0.05 was considered significant. Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA) and R programming version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient enrollment and baseline characteristics

The patient enrollment algorithm is shown in **Figure 1**. Among the 174 patients, 120 (69.0%) did not show preexisting AF at the time of the CRT implantation, and 54 had AF. Among 54 patients with previous AF, 29 patients had paroxysmal AF, and 25 patients had persistent AF. The patients without preexisting AF at pre-implantation were sub-classified according to whether they had device-detected AF during the follow-up period. Among the 120 patients without preexisting AF, 19 (15.8%) showed device-detected AF during a median follow-up of 25.1 months, and 7 of these patients were confirmed to have clinical AF using standard 12-lead ECG. Timing of first device-detected AF by interrogation from CRT implantation were median of 17.5 (Interquartile range, 12.5–24.3) months. The length of time over which the last interrogation was not significantly different between the device-detected AF and no-AF groups (27.3 [15.9–52.6] vs. 24.7 [15.0–49.0] months, p=0.914). The baseline characteristics according to the presence or absence of device-detected AF are shown in **Table 1**. The

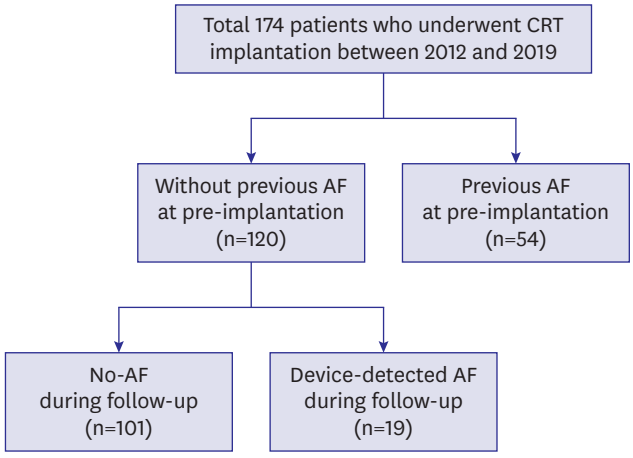

Figure 1. Patients enrollment algorithm.
AF = atrial fibrillation; CRT = cardiac resynchronization therapy.

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Table 1. The baseline characteristics of the device-detected AF and no-AF patients

	Total (n=120)	Device-detected AF (n=19)	No-AF (n=101)	p value
Clinical characteristics				
Age (years)	67 (59–74)	66 (59–69)	67 (58–75)	0.319
Male	64 (53.3)	11 (57.9)	53 (52.5)	0.854
BMI (kg/m^2)	23.4 (21.5–25.5)	24.3 (21.6–26.9)	23.0 (21.4–25.3)	0.302
NYHA class II	51 (42.5)	7 (36.8)	44 (43.6)	0.771
NYHA class III	69 (57.5)	12 (63.2)	57 (56.4)	0.771
SBP (mmHg)	114 (107–123)	107 (105–110)	114 (107–123)	0.071
DBP (mmHg)	68 (64–75)	63 (60–68)	68 (64–76)	0.057
Heart rate (bpm)	70 (63–76)	60 (59–71)	70 (64–77)	0.039
LBBB	93 (77.5)	13 (68.4)	80 (79.2)	0.369
QRS duration (ms)	167±19	169±23	167±18	0.759
QRS ≥150 ms	99 (82.5)	13 (68.4)	86 (85.1)	0.100
CRT-D	111 (92.5)	18 (94.7)	93 (92.0)	0.943
Ischemic etiology	18 (15.0)	4 (21.1)	14 (13.9)	0.483
Valvular heart disease	4 (3.3)	0 (0)	4 (4.0)	0.999
Hypertension	60 (50.0)	9 (47.4)	51 (50.5)	0.999
Diabetes mellitus	58 (48.3)	8 (42.1)	50 (49.5)	0.732
Chronic kidney disease	23 (19.2)	1 (5.3)	22 (21.9)	0.119
Stroke	14 (11.7)	0 (0)	14 (13.9)	0.122
Medication				
Beta-blocker	110 (91.7)	19 (100.0)	91 (90.1)	0.360
ACEi/ARB	119 (99.2)	18 (94.7)	101 (100.0)	0.158
MRA	95 (79.2)	15 (78.9)	80 (79.2)	0.999
AAD	10 (8.3)	3 (15.8)	7 (6.9)	0.195
OAC	30 (25.0)	7 (36.8)	23 (22.8)	0.247
Antiplatelet agent	58 (48.3)	9 (47.4)	49 (48.5)	0.999
Ivabradine	31 (25.8)	8 (42.1)	23 (22.8)	0.091
Laboratory data				
eGFR (mL/min/1.73 m^2)	73.0 (56.5–90.0)	75.0 (70.5–90.0)	73.0 (54.0–90.0)	0.173
NT-proBNP (pg/mL)	985 (397–2,586)	934 (602–2,215)	1,014 (368–2,635)	0.421
Log NT-proBNP	3.1±0.5	3.2±0.5	3.1±0.6	0.431
Troponin-T (pg/mL)	16 (10–28)	23 (13–35)	15 (10–25)	0.154
Echocardiographic parameters				
LVEF (%)	27 (22–32)	25 (22–28)	27 (22–32)	0.556
LAVI (mL/m^2)	41.0 (32.0–53.0)	48.0 (38.7–58.7)	39.0 (32.0–51.0)	0.056
LVESV (mL)	137 (103–176)	163 (111–222)	132 (103–170)	0.181

Values are expressed as the mean ± standard deviation, median (interquartile range), or numbers (%). Among the 174 patients, 120 (69.0%) had SR at the time of the CRT implantation,
AAD = anti-arrhythmic drug; ACEi = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BMI = body mass index; CRT-D = cardiac resynchronization therapy-defibrillator; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; LAVI = left atrial volume index; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; OAC = oral anticoagulation; SBP = systolic blood pressure.

median patient age was 67 years, and 53.3% of the patients without preexisting AF at pre-implantation were male. The median LVEF was 27%, and the median QRS duration was 167 milliseconds. There were no significant differences in comorbidities, medications, laboratory data, and echocardiographic parameters except for heart rate between the device-detected AF group and the no-AF group.

Differences in the clinical outcomes between the device-detected atrial fibrillation and no-atrial fibrillation groups

The CRT response and BiV pacing rates are presented in **Table 2** and **Figure 2**. There were no significant differences in the CRT response rate between the device-detected AF and no-AF groups at 6 months (63.2% vs. 73.3%, p=0.535). However, the BiV pacing percentage tended to be lower in the device-detected AF group than in the no-AF group (97.0% [95.2–98.9%]

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Table 2. Clinical outcomes of the device-detected AF and no-AF patients groups

Clinical outcomes	Device-detected AF (n=19)	No-AF (n=101)	p value
CRT responder at 6 months	12 (63.2)	74 (73.3)	0.535
CRT responder at 12 months*	7 (58.3)	50 (80.6)	0.131
Percentage of BiV pacing (%)	97.0 (95.2–98.9)	98.4 (98.0–99.0)	0.055
BiV pacing ≥98%	8 (42.1)	76 (75.2)	0.009
Heart failure hospitalization	8 (42.1)	14 (13.9)	0.007
Cardiovascular death	3 (15.8)	1 (1.0)	0.002
All-cause death	4 (21.1)	4 (4.0)	0.012
Appropriate ICD therapy†	4 (22.2)	8 (8.6)	0.130
Inappropriate ICD therapy†	4 (22.2)	4 (4.3)	0.010
Ischemic stroke	0 (0.0)	1 (1.0)	-

Values are expressed as the median (interquartile range) or numbers (%).
AF = atrial fibrillation; BiV = biventricular; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator.
*The CRT response at 12 months was evaluated for participants who had available echocardiography data (12 participants in the device-detected AF group and 62 participants in the no-AF group).
†Appropriate and inappropriate ICD therapy was evaluated only for the patients with CRT-defibrillator (18 participants in the device-detected AF group and 93 participants in the no-AF group).

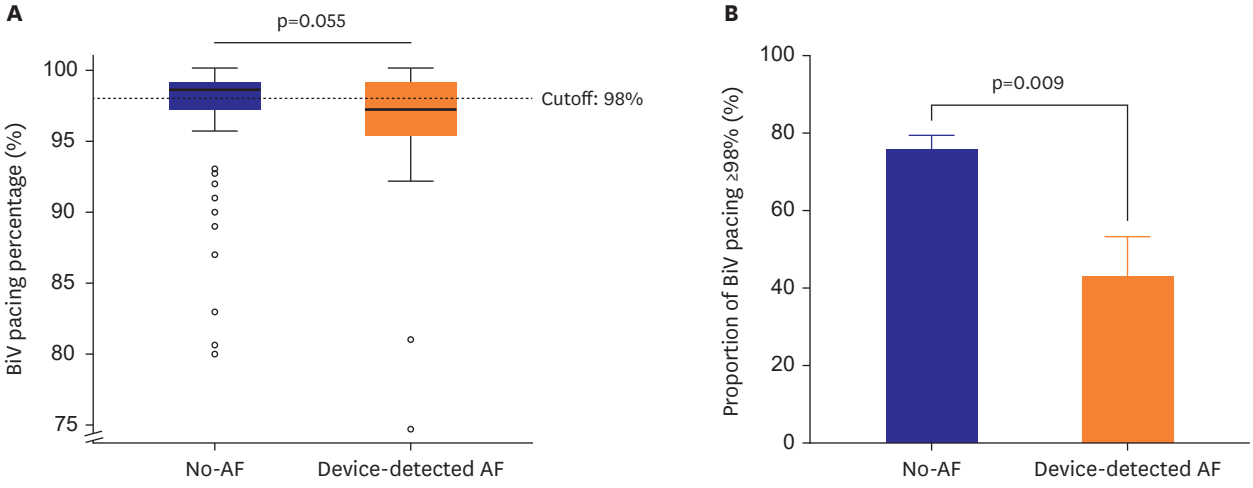

Figure 2. The BiV pacing rate according to device-detected AF in patients without preexisting AF at pre-implantation.
(A) BiV pacing percentage. (B) Proportion of optimal BiV pacing (≥98%). Error bars reflect standard errors.
AF = atrial fibrillation; BiV = biventricular.

vs. 98.4% [98.0–99.0%], p=0.055). The proportion of optimal BiV pacing (≥98%) was significantly lower in the device-detected AF group than in the no-AF group (42.1% vs. 75.2%, p=0.009). The Kaplan-Meier survival curves of the clinical outcomes according to the presence or absence of device-detected AF are shown in **Figure 3**. The device-detected AF group had a higher incidence of HF hospitalization than the no-AF group (log-rank p=0.007). Additionally, cardiovascular death and all-cause death were higher in the device-detected AF group than in the no-AF group (log-rank p=0.002 and p=0.012, respectively). There was no significant difference in the incidence of appropriate ICD therapy between the two groups (log-rank p=0.130). Inappropriate ICD therapy was higher in the device-detected AF group than in the no-AF group (log-rank p=0.010). Only one ischemic stroke occurred in the no-AF group during the follow-up period. After adjustment for age, sex, ischemic etiology, and LBBB, device-detected AF was associated with a higher incidence of HF hospitalization compared with no-AF (HF 3.05, CI 1.26-7.35, p=0.013). Also, the device-detected AF group, defined using an AHRE cutoff duration of 1 hour instead of 6 minutes, showed similar results to the main analysis (**Supplementary Figure 1**).

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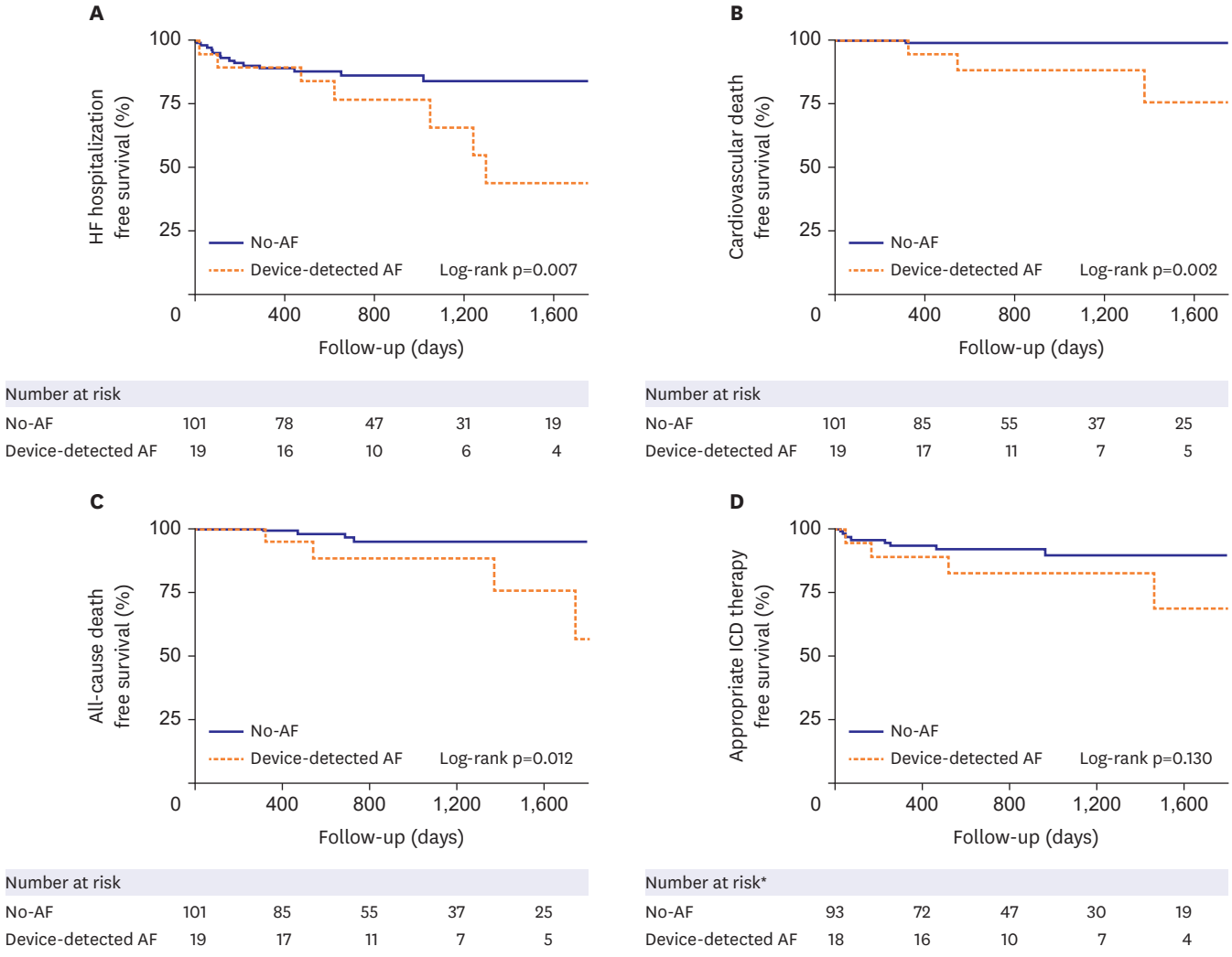

Figure 3. The Kaplan-Meier survival curves of the clinical outcomes between the device-detected AF and no-AF groups.
(A) HF hospitalization, (B) cardiovascular death, (C) all-cause death, and (D) appropriate ICD therapy.
AF = atrial fibrillation; CRT = cardiac resynchronization therapy; HF = heart failure; ICD = implantable cardioverter-defibrillator.
*Appropriate ICD therapy was evaluated only for the patients with CRT-defibrillator.

Differences in the clinical outcomes between the device-detected and previous atrial fibrillation groups

We compared the clinical outcomes between the device-detected and previous AF groups. The baseline characteristics are shown in **Supplementary Table 1**. The median age was significantly lower for the device-detected AF group than for the previous AF group (66 [59–60] vs. 71 [64–76], p=0.027). The N-terminal pro-brain natriuretic peptide level was significantly lower in the device-detected AF group than in the previous AF group (934 [602–2,215] pg/mL vs. 2,429 [1,260–6,687] pg/mL, p=0.035). Among the 54 patients with previous AF, 21 (38.9%) underwent AVNA within 1 month after the CRT implantation. There were no significant differences in the medications or medical histories between the two groups.

The CRT response and BiV pacing rates for the device-detected AF and previous AF groups are presented in **Table 3** and **Supplementary Figure 2**. The device-detected AF group showed no significant differences in the CRT response rate at 6 and 12 months compared with the

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Table 3. Clinical outcomes of each AF groups

Clinical outcomes	Device-detected AF (n=19)	Previous AF (n=54)	p value
CRT responder at 6 months	12 (63.2)	27 (50.0)	0.471
CRT responder at 12 months*	7 (58.3)	17 (48.6)	0.803
Percentage of BiV pacing (%)	97.0 (95.2–98.9)	98.6 (96.0–99.3)	0.191
BiV pacing ≥98%	8 (42.1)	34 (63.0)	0.189
Heart failure hospitalization	8 (42.1)	20 (37.0)	0.776
Cardiovascular death	3 (15.8)	5 (9.3)	0.706
All-cause death	4 (21.1)	7 (13.0)	0.864
Appropriate ICD therapy†	4 (22.2)	4 (8.0)	0.213
Inappropriate ICD therapy†	4 (22.2)	3 (6.0)	0.199
Ischemic stroke	0 (0.0)	3 (5.6)	-

Values are expressed as the median (interquartile range) or numbers (%).
AF = atrial fibrillation; BiV = biventricular; CRT = cardiac resynchronization therapy = ICD = implantable cardioverter-defibrillator.
*The CRT response at 12 months was evaluated for participants who had available echocardiography data (12 participants in the device-detected AF group and 35 participants in the previous AF group).
†Appropriate and inappropriate ICD therapy was evaluated only for the patients with CRT-defibrillator (18 participants in the device-detected AF group and 50 participants in the no-AF group).

previous AF group (63.2% vs. 50.0%, p=0.471; 58.3% vs. 48.6%, p=0.803). The BiV pacing percentage was 97.0% (95.2%–98.9%) and 98.6% (96.0%–99.3%) for each group, which was not significantly different (p=0.191). The proportion of optimal BiV pacing (≥98%) was not significantly different between the groups (42.1% vs. 63.0%, p=0.189).

The Kaplan-Meier survival curves of the clinical outcomes for the device-detected and previous AF groups are shown in **Figure 4**. There were no significant differences in HF hospitalization, cardiovascular death, all-cause death, and appropriate/inappropriate ICD therapy between the two groups (all log-rank p>0.05). Three cases of ischemic stroke occurred in the previous AF group during the follow-up period. Also, there were no significant difference in clinical outcomes between device-detected AF and previous paroxysmal AF (**Supplementary Figure 3**).

Of the 19 device-detected AF patients, 7 (36.8%) received rhythm control therapy during the follow-up period to maintain optimal BiV pacing (**Supplementary Table 2**). Among these seven patients, 6 patients were administered anti-arrhythmic drugs, and one underwent radiofrequency catheter ablation during the follow-up period. Seven (36.8%) patients received aggressive rate control therapy, including up-titration of beta-blockers, and one (5.2%) underwent AVNA during the follow-up period. Of the 54 patients with previous AF, 24 (44.4%), and 8 (14.8%) patients received rhythm control therapy, and aggressive rate control therapy, respectively. Among the 24 patients who received rhythm control therapy, 19 received anti-arrhythmic drugs, and 5 underwent AF radiofrequency catheter ablation. Among 54 patients with previous AF, 24 (44.4%) received AVNA at pre-implantation and/or during the follow-up period, and they could be treated with rhythm control or rate control prior to AVNA.

DISCUSSION

The main findings of the present study are as follows: 1) The patients with device-detected AF showed lower optimal BiV pacing and worse clinical outcomes than those without AF. 2) There were no significant differences in the optimal BiV pacing (≥98%) and clinical outcomes between the device-detected AF and the previous AF groups.

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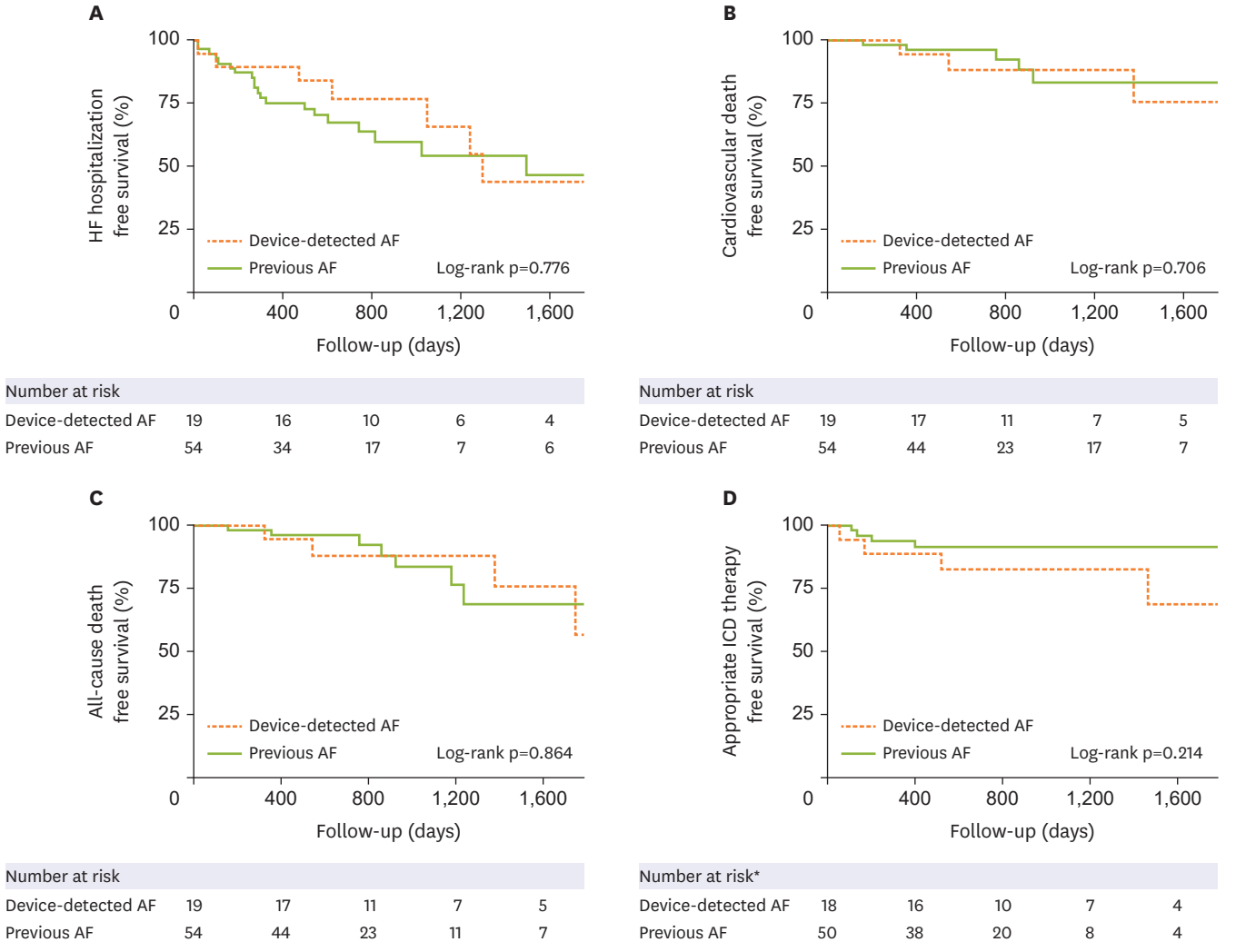

Number at risk					
Device-detected AF	19	16	10	6	4
Previous AF	54	34	17	7	6

Number at risk					
Device-detected AF	19	17	11	7	5
Previous AF	54	44	23	17	7

Number at risk					
Device-detected AF	19	17	11	7	5
Previous AF	54	44	23	11	7

Number at risk*					
Device-detected AF	18	16	10	7	4
Previous AF	50	38	20	8	4

Figure 4. The Kaplan-Meier survival curves of the clinical outcomes for the patients in each AF groups.
(A) HF hospitalization, (B) cardiovascular death, (C) all-cause death, and (D) appropriate ICD therapy.
AF = atrial fibrillation; AVNA = atrioventricular nodal ablation; CRT = cardiac resynchronization therapy; HF = heart failure; ICD = implantable cardioverter-defibrillator.
*Appropriate ICD therapy was evaluated only for the patients with CRT-defibrillator.

Considering that the definitions of device-detected and subclinical AF and the follow-up periods differ in various studies, the rate of device-detected AF could vary. Also, the differences in the baseline characteristics (e.g., age, sex, comorbidities, and LVEF) in each study can affect the occurrence of device-detected AF during the follow-up period. In our study, the rate of device-detected AF during the follow-up period for the participants without preexisting AF at CRT pre-implantation was 15.8%. Previous studies have shown an average incidence of 20–30% for device-detected AF during the follow-up period.[11-13)20)] The slightly lower incidence in our study may be because of a higher AF detection rate before the CRT implantation, since many participants performed 24 hours of Holter monitoring before implantation.

Although device-detected or subclinical AF can be overlooked, its importance in clinical outcomes for patients with cardiac implantable electronic devices has received attention recently. Healey et al.[21)] showed that subclinical AF is associated with an increased risk of ischemic stroke in patients with pacemakers or ICDs. Subclinical AF progression may also be

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associated with an increased risk of HF hospitalization.[22] Device-detected AF can interfere with adequate BiV pacing; therefore, recent studies have focused on the clinical effect of device-detected AF in patients who have undergone CRT.[11-13] Our study coincides well with these studies and has the advantage of evaluating the association of device-detected AF with various clinical outcomes, including HF hospitalization, cardiovascular death, all-cause death, and appropriate ICD therapy. Additionally, we showed that device-detected AF is associated with lower optimal BiV pacing than no-AF.

In our study, patients with device-detected AF or previous AF had a significantly higher event rates than patients with AF enrolled in the CERTIFY study.[23] Even compared with the AF patients without AVNA in the CERTIFY study, the patients with device-detected or previous AF in our study had much higher event rates. We assumed that this was one of the reasons why the device-detected AF groups had a worse prognosis than the no-AF group.

Recent studies have shown that effective BiV pacing is important for successful CRT.[7-9] Poor BiV pacing could be caused by premature ventricular complex, atrial tachyarrhythmia, or inappropriately programmed long atrioventricular delay in our study, and previous study showed that atrial tachyarrhythmia might be the most common cause of CRT pacing loss.[24] The ideal effective cutoff for the BiV pacing rate has increased in recent studies. Koplan et al.[8] demonstrated that BiV pacing >92% is associated with a 44% reduction in the composite endpoint (all-cause mortality and HF hospitalization), and Hayes et al.[7] showed that BiV pacing ≥98% and increasing BiV pacing percentage trends are associated with reductions in mortality. This suggests that BiV pacing should be kept as close to 100% as possible[1)14)]; therefore, we defined the optimal BiV pacing percentage as ≥98% considering previous studies. Our results show that the proportion of optimal BiV pacing (≥98%) was significantly lower in the device-detected AF group. Because the distribution of the BiV pacing percentage has not generally followed a normal distribution, the comparison with the mean BiV pacing percentage value used in previous studies may be less effective for statistical analyses.[12] Our study may imply that obtaining the optimal BiV pacing is more important for benefits of CRT rather than BiV pacing percentage itself. However, this small observational study could not draw exact causal relationship between optimal BiV pacing and adverse clinical outcomes. Left atrial reverse remodeling after CRT implantation, which could be affected by AF, might be associated with clinical outcomes.[25)26)]

In our study, device-detected AF patients received rhythm control therapy (36.8%) or aggressive rate control therapy (36.8%) during the follow-up period to obtain the optimal BiV pacing. Seven patients who were on suboptimal β-blocker doses at baseline received up-titration during the follow-up period. Despite these aggressive treatments, device-detected AF patients showed worse clinical outcomes and lower optimal BiV pacing than the no-AF patients. This may be due to delayed recognition of device-detected AF or the deleterious effect of hidden AF burden. Also, the device-detected AF group showed similar clinical outcomes and optimal BiV pacing compared with the previous AF group. Therefore, it may be important to immediately assess and manage device-detected AF during the follow-up period.

For CRT patients with AF, adequate BiV pacing can be achieved using AVNA. AVNA for AF patients implanted with CRT is associated with lower HF hospitalization and mortality rates.[27)28)] Therefore, AVNA should be considered for AF patients with incomplete BiV pacing.[1)] In our study, among the 54 patients with previous AF, 21 (38.9%) underwent AVNA within 1 month after the CRT implantation. Moreover, the previous AF group received rhythm

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control therapy (44.4%) or aggressive rate control therapy (14.8%) to maintain the optimal BiV pacing at pre-implantation and/or during the follow-up period. This may explain our unanticipated finding that the clinical outcomes were similar between the device-detected AF and previous AF groups. However, the previous study on the benefits of AVNA focused primarily on preventing a decrease in the BiV pacing rate for pre-implantation AF patients, and not for device-detected AF patients. Further large studies to evaluate the benefits of AVNA for device-detected AF patients will be interesting.

This study has several limitations. First, this was a retrospective, single-center study with a small sample size. Our results are limited by the small number of cases and outcomes. Also, a lack of statistical significance between groups at baseline does not automatically mean that there are no confounder effects on results. While not statistically significant, patients with device-detected AF group had a lower incidence of left bundle branch block (68.4% vs. 80.2%, p=0.369), which is one of the powerful predictors of CRT response. Our study should be supported by further large prospective studies. Second, the average percentage of BiV pacing throughout the follow-up was derived from the last interrogation, so we could not have information on BiV pacing at different time throughout the study, as previously reported.[9] Device-detected AF could occur at any time during the follow-up period, therefore it is difficult to discriminate whether device-detected AF was cause or effect of poor CRT response. This could be one of the major limitation in interpreting our results. Third, different CRT device manufacturers used slightly different algorithms for AF detection and CRT optimization. Fourth, the real BiV pacing rate could be different from the device-reported value because of fusion/pseudofusion beats. Also, BiV pacing rates could be overestimated to a greater extent in patients with device-detected AF or previous AF than in patients with no-AF because fusion/pseudofusion beats are more likely to occur during AF than SR.[29][30] Fifth, we could not analyze the CRT response defined as a decrease in the LVESV ≥15% serially during long term follow-up period. Sixth, after the development of device-detected AF during the follow-up, some patients received rhythm control or aggressive rate control treatments, but we could not compare the effect of these treatments on the clinical outcomes. Seventh, we could not evaluate the impact of the AF burden on clinical outcomes, although an increased AF burden is associated with increased HF morbidities in CRT patients.[10] Eighth, not all participants underwent 24-hour Holter monitoring before CRT implantation: Only 53 (43.8%) patients without pre-existing AF at CRT implantation underwent Holter, and the time interval between Holter and CRT implantation was widely distributed from 0 days to 5 years. Despite these limitations, our study has the advantage of evaluating the association of device-detected AF with optimal BiV pacing and various clinical outcomes. Further large prospective studies are required to determine the relationship between device-detected AF and/or AF burden and clinical outcomes in patients treated with CRT.

In conclusion, for HF patients implanted with CRT, device-detected AF was associated with lower optimal BiV pacing and worse clinical outcomes than no-AF.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

The baseline characteristics of the patients in each AF groups

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Supplementary Table 2

Therapy to maintain the optimal BiV pacing

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Supplementary Figure 1

The Kaplan-Meier survival curves of the clinical outcomes between the device-detected AF and no-AF groups using a cutoff duration of 1 hour instead of 6 minutes.

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Supplementary Figure 2

The BiV pacing rate of each AF groups.

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Supplementary Figure 3

The Kaplan-Meier survival curves of the clinical outcomes for the patients with device-detected AF and previous PAF.

Click here to view

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