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Original Research

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Real-World Effectiveness of Adaptive Left Ventricular-Only Pacing for Cardiac Resynchronization Therapy in Asian Population: Insights From the K-Adaptive CRT Study

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AUTHOR'S SUMMARY

Previous studies on the advantages of adaptive left ventricular-only pacing (LVP) compared to conventional biventricular pacing (BVP) for cardiac resynchronization therapy (CRT), have shown mixed results in patients with heart failure (HF). Most investigations into CRT with adaptive LVP have predominantly involved Western patients, which makes it challenging to directly apply those findings to the Asian patient population. This study, the largest adaptive CRT study in Asian HF patients to date, demonstrates that adaptive LVP significantly reduces the risk of all-cause death, HF hospitalization, and appropriate implantable cardioverter-defibrillator therapy when compared to conventional BVP.

ABSTRACT

Background and Objectives: Conflicting results have been reported regarding the efficacy of left ventricular-only pacing (LVP) synchronized with intrinsic right ventricular conduction (adaptive LVP) for cardiac resynchronization therapy (CRT) in Western heart failure (HF) populations. We compared adaptive LVP with conventional biventricular pacing (BVP) in Asian HF patients.
Methods: The K-adaptive CRT study, the largest adaptive CRT study to date in Asian HF patients, evaluated 368 HF patients who received CRT devices with an adaptive pacing algorithm between September 2013 and March 2020 from 25 tertiary hospitals in Korea. Patients were classified into 3 groups according to their pacing configuration: adaptive LVP (n=160), adaptive BVP (n=86), and conventional BVP groups (n=122). Primary outcome was the composite of all-cause death, HF hospitalization, and appropriate implantable cardioverter-defibrillator therapy.

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Conflict of Interest
Seung Jung Park has served as a speaker for and received research grants from Boston Scientific, Biotronik, Abbott, and Medtronic. Kyoung-Min Park received research grants from Boston Scientific. Young Keun On received research grants from Bayer AG, Daiichi Sankyo Company. Boyoung Joung has served as a speaker for Bayer, BMS/Pfizer, Medtronic, and Daiichi-Sankyo and received research funds from Medtronic and Abbott. The remaining authors have no other relationships or activities that could appear to have influenced the submitted work.

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

Author Contributions
Conceptualization: Gwag HB, Joung B, Park SJ; Data curation: Gwag HB, Lee SH, Kim J, Kim JY, Park SJ; Formal analysis: Gwag HB, Lee SH, Kim TH, Kim J, Park SJ; Funding acquisition: Park KM, Joung B, Park SJ; Investigation: Gwag HB, Kim JY, Park KM, Joung B, Park SJ; Methodology: Gwag HB, Kim TH, Park KM, On YK, Joung B, Park SJ; Project administration: Gwag HB, On YK, Park SJ; Resources: Gwag HB, Kim TH, Kim J, Kim JY, Park KM, On YK, Park SJ; Software: Gwag HB, Lee SH, Kim TH, Kim J, Kim JY, Park SJ; Supervision: On YK,

Results: During the mean 3.7-year follow-up period, incidence of the primary outcome was significantly lower in the adaptive LVP group than the conventional BVP group (hazard ratio [HR], 0.56; 95% confidence interval [CI], 0.36–0.85; p=0.007), while outcomes in the adaptive and conventional BVP groups were comparable. Patients with higher LVP% (≥65%) showed a further reduction in relative risk of the primary outcome (HR, 0.41; 95% CI, 0.22–0.76; p=0.005). Adaptive LVP was consistently associated with a lower risk of clinical outcomes in various subgroup analyses, and was identified as an independent factor for favorable long-term outcomes.
Conclusions: The K-adaptive CRT study suggests that adaptive LVP is associated with better clinical outcomes than conventional BVP in Asian HF patients.

Keywords: Heart failure; Cardiac resynchronization therapy; Adaptive pacing; Asian

INTRODUCTION

To maximize treatment response, current devices for cardiac resynchronization therapy (CRT) have automated optimization algorithms that adjust atrio-ventricular (AV) and ventriculo-ventricular (VV) delays in response to dynamical changes in intrinsic cardiac conduction. These algorithms, which are known to be convenient and time-saving, have shown comparable or better performance in various clinical endpoints than echocardiography-based optimization.[1-3] Among them, the AdpativCRT algorithm (aCRT) (Medtronic Inc., Minneapolis, MN, USA) can provide left ventricular (LV)-only pacing (LVP) synchronized to intrinsic right ventricular (RV) activation (adaptive LVP) when the intrinsic AV delay is ≤200 ms and the patients are in sinus rhythm at ≤100 bpm; in other scenarios, the algorithm provides biventricular pacing (BVP) with either dynamic AV/VV optimization (adaptive BVP) or fixed AV/VV delays (conventional BVP).

Several previous clinical studies have reported that aCRT-based pacing is associated with a significantly higher clinical response rate, accordingly reducing the 30-day readmission rate, incidence of new-onset atrial fibrillation (AF), and composite event of overall mortality and heart failure hospitalization (HFH) in comparison with conventional BVP.[1)4-6)] However, previous studies predominantly enrolled patients from Western populations. Few real-world studies have included Asian patients.[7-11)] Moreover, a recent trial reported that adaptive LVP did not improve clinical outcomes compared to conventional CRT.[12)] Therefore, we aimed to evaluate the clinical effectiveness of aCRT-based pacing compared to conventional BVP in Asian heart failure (HF) patients in the setting of a real-world, multicenter study.

METHODS

Ethical statement

The study was approved by the Institutional Review Boards (IRB) of the core center (IRB No. 2018-07-164: 2020-04-006) and all other participating hospitals. The study protocol conforms to the ethical guidelines of the 2013 Declaration of Helsinki. Written informed consent was waived because of the retrospective study design and anonymized data.

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Joung B, Park SJ; Validation: Gwag HB, Kim JY, Park KM, Joung B, Park SJ; Visualization: Gwag HB, Lee SH, Kim TH, Park SJ; Writing - original draft: Gwag HB, Lee SH, Kim TH, Joung B, Park SJ; Writing - review & editing: Park SJ.

Study design and patient population

The Korean Adaptive CRT (K-adaptive CRT) study was designed as a multicenter retrospective study including 25 tertiary hospitals in Korea to evaluate the real-world clinical effectiveness of the adaptive LVP or BVP versus conventional BVP. This investigation builds upon a pilot study conducted by the core laboratory (Samsung Medical Center) of the present study.[11] This study was supported by Medtronic, however, the funder was not involved in the study design, data collection, or analysis of data, and was allowed limited access to the raw data only when some verification was required.

Patients met all of the following inclusion criteria to be eligible for this study: 1) implantation of an aCRT-capable CRT device between September 2013 and March 2020, 2) LV ejection fraction ≤35%, and 3) New York Heart Association (NYHA) class II, III, or ambulatory IV. We excluded patients with 1) generator replacement, 2) persistent or permanent AF, 3) insufficient information on CRT pacing configurations, 4) pre-CRT narrow QRS duration (<120 ms), or 5) CRT inactivation, follow-up loss, or death within 3 months after CRT implantation (**Figure 1**).

Data collection

Data on baseline characteristics and follow-up clinical outcomes were collected through careful review of electronic medical records (**Tables 1** and **2**). The attending physician at each participating center completed a case report form with aid from the clinical research associates of the core center, who visited participating centers for source data verification. Direct patient identifiers including names, personal registration numbers, and medical record numbers were replaced by linking codes. Device interrogation data, scanned images of 12-lead electrocardiograms (ECGs), and final fluoroscopic images of the LV leads were collected separately and sent to the core center to be analyzed.

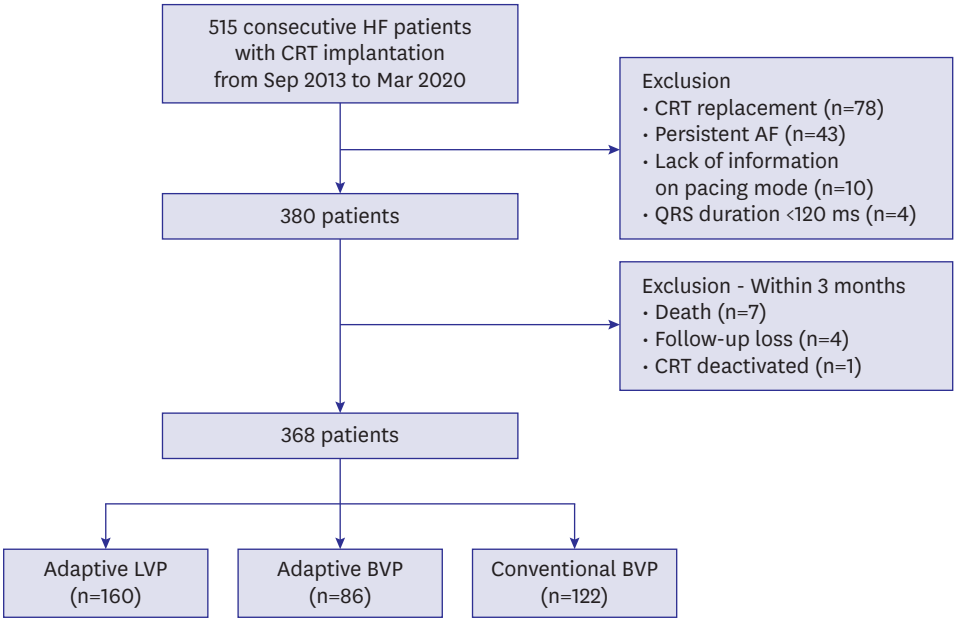

Figure 1. Study flow.
AF = atrial fibrillation; BVP = biventricular pacing; CRT = cardiac resynchronization therapy; HF = heart failure; LVP = left ventricular-only pacing.

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Table 1. Baseline characteristics

	Total (n=368)	Adaptive LVP (n=160)	Adaptive BVP (n=86)	Conventional BVP (n=122)	p value*
Age (years)	66.4±12.1	66.8±11.7	67.2±12.9	65.2±12.0	0.429
Male	226 (61.4)	96 (60.0)	51 (59.3)	79 (64.8)	0.647
Height (cm)	162.0±9.1	160.9±8.8	162.8±9.6	162.7±9.0	0.164
Body mass index (kg/m^2)	23.8±3.8	23.7±3.8	24.0±4.0	23.9±3.6	0.798
NYHA functional class					
II	81 (22.0)	37 (23.1)	20 (23.3)	24 (19.7)	0.747
III or IV	287 (78.0)	123 (76.9)	66 (76.7)	98 (80.3)	
Etiology of cardiomyopathy					
Ischemic	66 (17.9)	28 (17.5)	22 (25.6)	16 (13.1)	0.068†
Non-ischemic	302 (82.1)	132 (82.5)	64 (74.4)	106 (86.9)	
Medical history					
Hypertension	210 (57.1)	87 (54.4)	57 (66.3)	66 (54.1)	0.143
Diabetes	162 (44.0)	75 (46.9)	41 (47.7)	46 (37.7)	0.227
Chronic renal insufficiency	85 (23.1)	40 (25.0)	18 (20.9)	27 (22.1)	0.734
Stroke	36 (9.8)	15 (9.4)	11 (12.8)	10 (8.2)	0.533
Myocardial infarction	37 (10.1)	16 (10.0)	10 (11.6)	11 (9.0)	0.826
Paroxysmal atrial fibrillation	59 (16.0)	21 (13.1)	15 (17.4)	23 (18.9)	0.396
Medication					
Beta blocker	285 (77.4)	124 (77.5)	61 (70.9)	100 (82.0)	0.172
RAAS inhibitor or ARNI	321 (87.2)	141 (88.1)	78 (90.7)	102 (83.6)	0.289
MRA	260 (70.7)	119 (74.4)	54 (62.8)	87 (71.3)	0.161
Diuretics	317 (86.1)	138 (86.3)	72 (83.7)	107 (87.7)	0.714
Electrocardiographic findings					
PR interval (ms)	193.3±40.8	189.3±32.7	200.4±50.9	194.3±43.6	0.167
LBBB morphology	308 (83.7)	143 (89.4)	65 (75.6)	100 (82.0)	0.017§
QRS duration (ms)	167.3±22.3	164.2±19.1	169.4±25.6	170.0±23.3	0.059‡
QRS duration ≥150 msec	290 (78.8)	123 (76.9)	66 (76.7)	101 (82.8)	0.420
QRS duration/height (ms)	1.03±0.14	1.02±0.12	1.04±0.15	1.05±0.15	0.296
Echocardiographic findings					
LV ejection fraction (%)	24.7±6.2	24.3±6.0	25.1±5.8	24.8±6.7	0.580
LV end diastolic dimension (mm)	66.6±8.9	67.2±8.9	65.8±8.4	66.5±9.2	0.521
LV end systolic dimension (mm)	57.2±9.9	58.5±9.8	55.5±9.2	56.6±10.4	0.057§
LV end diastolic volume (mL)	206.8±78.0	214.8±80.3	191.4±75.3	208.0±76.2	0.144§
LV end systolic volume (mL)	155.7±66.7	161.3±66.0	144.9±63.4	156.9±70.0	0.280
Type of CRT					
CRT-defibrillator	359 (97.6)	157 (98.1)	82 (95.3)	120 (98.4)	0.316
CRT-pacemaker	9 (2.4)	3 (1.9)	4 (4.7)	2 (1.6)	
LV lead position in RAO					
Non-apical	350 (95.1)	151 (94.4)	81 (94.2)	118 (96.7)	0.599
Apical	18 (4.9)	9 (5.6)	5 (5.8)	4 (3.3)	
LV lead position in LAO					
Lateral	360 (97.8)	152 (95.0)	86 (100)	122 (100)	0.005‡§
Non-lateral	8 (2.2)	8 (5.0)	0 (0)	0 (0)	
CRT pacing percentage (%)	99.3±3.4	99.8±0.5	98.9±2.8	99.0±5.3	0.074§

Data are presented as mean ± standard deviation or as number (%).
ARNI = angiotensin receptor neprilysin inhibitor; BVP = biventricular pacing; CRT = cardiac resynchronization therapy; LAO = left anterior oblique; LBBB = left bundle branch block; LV = left ventricular; LVP = left ventricular pacing; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; RAAS = renin angiotensin aldosterone system; RAO = right anterior oblique.
*The p value refers to the difference among the 3 groups by analysis of variance.
The p value <0.05 between the †conventional BVP vs. adaptive BVP, ‡conventional BVP vs. adaptive LVP, and §adaptive BVP vs. adaptive LVP groups.

Classification of patient groups according to pacing configuration

Patients were classified into 3 groups according to the programmed pacing configurations, as determined by the discretion of the attending physicians: 1) conventional BVP (BVP with fixed AV/VV delays), 2) adaptive BVP (BVP with dynamic AV/VV optimization), and 3) adaptive LVP (RV-synchronized LV-only pacing) groups. Additionally, patients in the adaptive LVP group were further stratified into 2 subgroups based on the percentage of adaptive LVP pacing, using the median value as the cutoff. For patients receiving conventional BVP, CRT

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Table 2. Primary and secondary outcomes at the mean follow-up

	Adaptive LVP (n=160)	Adaptive BVP (n=86)	Conventional BVP (n=122)	p value*
Primary outcome				
All-cause death, heart failure hospitalization, and appropriate ICD therapy	37 (26.6)	37 (48.8)	50 (43.6)	0.003†‡
Secondary outcomes				
All-cause death	8 (6.3)	14 (20.8)	17 (15.9)	0.009†‡
Cardiac death	4 (3.5)	10 (15.6)	10 (9.7)	0.013†‡
HF hospitalization	32 (23.5)	25 (33.1)	34 (31.3)	0.207
Appropriate ICD therapy	9 (6.2)	11 (14.1)	22 (18.7)	0.007†
All-cause death or HF hospitalization	34 (24.8)	31 (41.8)	39 (35.1)	0.041‡
Cardiac death or HF hospitalization	32 (23.5)	29 (40.0)	35 (32.3)	0.057

Values are presented as number (%).
BVP = biventricular pacing; HF = heart failure; ICD = implantable cardioverter-defibrillator; LVP = left ventricular pacing.
*The p value refers to the difference among the 3 groups by log-rank test.
The p value <0.05 between †the adaptive LVP vs conventional BVP, or ‡adaptive LVP vs. adaptive BVP groups.

optimization was performed using either ECG- or echocardiography-based methods, as determined by the attending physicians at each participating center. Reprogramming of pacing configurations occurred in 34 patients (9.2%) during the follow-up period. In these cases, patients were classified by the pacing modes maintained for the longest period. Representative pacing modes of those 34 patients were utilized for an average of 74% of their entire follow-up period.

Definition and study outcomes

QRS morphology was reviewed by a core laboratory and classified as either left bundle branch block (LBBB) or non-LBBB type. LBBB was defined as 1) QRS duration ≥130 ms, 2) QS or rS in lead V1 and V2, and 3) mid-QRS notching or slurring in 2 or more of leads V1, V2, V5, V6, I, and aVL.[13] CRT pacing percentage was calculated as the average of BVP percentages in the conventional and adaptive BVP groups or as the average of LVP plus BVP percentages in the adaptive LVP group over the first year of the follow-up period. The primary outcome was the composite of all-cause death, HFH, and appropriate implantable cardioverter-defibrillator (ICD) therapy. Secondary outcomes included each component of the primary outcome, cardiac death, the composite of all-cause death and HFH, and the composite of cardiac death and HFH (**Table 2**). HFH was defined according to the 2016 European Society of Cardiology guidelines following careful evaluation of HF symptoms or signs, pulmonary congestion on chest radiography, objective findings of cardiac dysfunction by echocardiography, and cardiac biomarker levels.[14] All deaths were considered to be cardiac unless a definitive noncardiac cause could be identified. Appropriate ICD therapy was defined as anti-tachycardia pacing therapy or shock for ventricular tachyarrhythmia determined by the clinical and device information.

Statistical analysis

Continuous variables were reported as means ± standard deviation or medians with interquartile ranges, and categorical variables as numbers (percentages). Comparisons among ≥3 groups were performed using analysis of variance and Pearson's χ^2 test as appropriate. Clinical outcomes were analyzed using the Kaplan-Meier method and compared with the log-rank test. Considering the impact of PR interval and QRS morphology on CRT response, the primary outcome was also compared in a subset of patients with normal PR intervals and LBBB morphology. Furthermore, various subgroup analyses were performed according to age category, sex, height, body mass index (BMI), HF etiology, several ECG variables, and LV size. Cox proportional hazard regression models were used to determine independent predictors of the primary outcome. We included variables previously identified

as clinically significant predictors for CRT response in our multivariate analysis. To mitigate overfitting, we initially limited the number of covariates by applying a significance threshold of p<0.05 in the univariate analysis. Additionally, we tested several multivariate models including extra variables such as age, sex, LV ejection fraction, and NYHA functional class regardless of their univariate significance, as well as a model that incorporated all clinically relevant variables using a non-parsimonious approach. Two-sided p values <0.05 were considered significant and all analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics of patients

A total of 515 patients received a CRT device equipped with the aCRT algorithm during the study period. Three hundred sixty-eight consecutive patients were finally analyzed for the study after excluding 147 patients for various reasons as shown in **Figure 1**. Conventional BVP, adaptive BVP, and adaptive LVP groups had 122, 86, and 160 patients, respectively (**Figure 1**). Clinical variables including age, sex, height, BMI, NYHA class, previous medical history, and utilization of HF medications were not significantly different among the 3 groups. Most LV leads were implanted in non-apical and lateral LV walls in all 3 groups with high CRT pacing percentages (>98%). The adaptive LVP group had the highest prevalence of LBBB and the largest LV dimensions, while the conventional BVP group had the lowest rate of ischemic cardiomyopathy and the most frequent prescription of beta-blockers (**Table 1**).

Clinical outcomes in total patients

During the mean follow-up period of 3.7±2.1 years, the primary composite outcome occurred in 124 (33.7%) patients. The adaptive LVP group showed a significantly lower incidence of the primary outcome than the other 2 groups (**Table 2**, **Figure 2A**). With the conventional BVP group as a reference, the hazard ratio (HR) of the primary outcome in the adaptive LVP group was 0.56 with a 95% confidence interval (CI) of 0.36–0.85 (p=0.007). The adaptive LVP group also had the lowest incidence of any secondary outcome. When patients in the adaptive LVP group were stratified into 2 subgroups by the median LVP percentage (adaptive LV ≥65% or <65%), there was a further reduction in the HR of the composite primary outcome of the adaptive LVP ≥65% subgroup (HR, 0.41; 95% CI, 0.22–0.76; p=0.005), while the adaptive LVP <65% subgroup tended to show better outcome than the conventional BVP group. In contrast, the adaptive BVP group had a long-term prognosis similar to that of the conventional BVP group (**Figure 2A and B**).

Clinical outcomes in various subgroups and multivariable analysis for the primary outcome

The adaptive LVP group showed a consistently lower incidence of the primary outcome than the other groups, even when patients with LBBB morphology and normal PR interval (≤200 ms) were analyzed separately (**Figure 2C**, **Supplementary Table 1**). In forest plot subgroup analysis, both conventional and adaptive BVP groups were combined as the BVP group considering the similar pacing configurations and long-term prognoses of the 2 groups. Adaptive LVP was consistently associated with more favorable clinical outcome in most subgroups than the BVP group, but a significant interaction was observed between pacing configuration (BVP or LVP) and LBBB morphology, suggesting better performance of adaptive LVP in LBBB patients (**Figure 3**).

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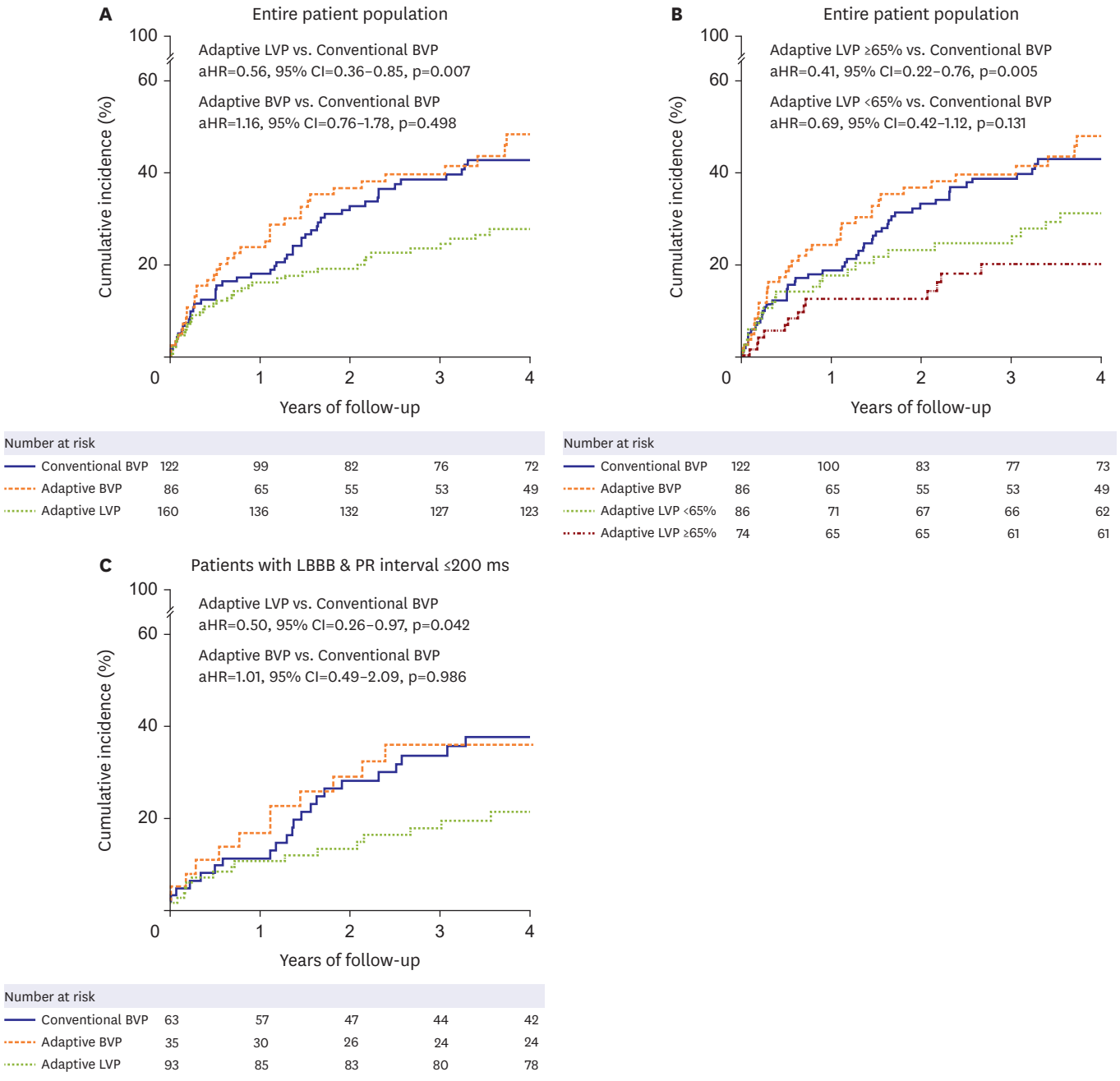

Figure 2. Kaplan-Meier estimates of time to primary outcome according to pacing configuration (A) and pacing configuration and LVP percentage (B) in the total population. Survival curves for the primary outcome were compared in patients with LBBB and PR interval ≤200 ms (C). The primary outcome was the composite of all-cause death, heart failure hospitalization, and appropriate implantable cardioverter-defibrillator therapy. The conventional BVP group was the reference.
aHR = adjusted hazard ratio; BVP = biventricular pacing; CI = confidence interval; LBBB = left bundle branch block; LVP = left ventricular pacing.

We also performed several sensitivity analyses for the primary composite outcome using different study populations. The favorable outcome of adaptive LVP was consistent even when 12 patients who were previously excluded due to death, follow-up loss, or switched-off CRT pacing within 3 months were included (HR, 0.55; 95% CI, 0.36–0.82; p=0.004; **Supplementary Figure 1**). In addition, the adaptive LVP group still showed better outcomes than the other groups, whether the 34 patients with a reprogrammed pacing configuration

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Subgroup	Adaptive LV	Conventional or Adaptive BVP	Hazard ratio (95% CI)	p value
	Number of events / Total number of patients (cumulative incidence, %)			
Age				
<65 years	11/55 (21.9%)	32/79 (42.3%)	0.58 (0.30–1.12)	0.741
≥65 years	26/105 (29.3%)	55/129 (48.0%)	0.56 (0.35–0.89)	
Sex				
Male	25/96 (30.2%)	55/130 (46.2%)	0.65 (0.41–1.04)	0.310
Female	12/64 (21.6%)	32/78 (44.6%)	0.44 (0.23–0.86)	
Height				
<170 cm	30/134 (25.6%)	64/151 (46.2%)	0.51 (0.33–0.79)	0.378
≥170 cm	7/26 (33.7%)	23/57 (44.0%)	0.67 (0.29–1.55)	
BMI				
<25 kg/m²	24/111 (25.4%)	59/135 (49.2%)	0.44 (0.27–0.71)	0.178
≥25 kg/m²	13/49 (29.9%)	28/73 (39.5%)	0.79 (0.41–1.53)	
Etiology of heart failure				
ICMP	12/28 (47.8%)	17/38 (50.3%)	1.02 (0.49–2.14)	0.059
NICMP	25/132 (22.2%)	70/170 (44.5%)	0.48 (0.30–0.75)	
PR interval				
≤200 msec	24/104 (27.0%)	43/113 (41.2%)	0.60 (0.37–0.99)	0.932
>200 msec	12/47 (27.7%)	23/61 (43.6%)	0.70 (0.35–1.40)	
QRS duration				
<150 msec	14/37 (47.4%)	23/41 (60.7%)	0.76 (0.40–1.47)	0.328
≥150 msec	23/123 (21.2%)	64/167 (41.8%)	0.48 (0.30–0.77)	
QRS morphology				
LBBB	26/143 (21.2%)	61/165 (39.7%)	0.51 (0.33–0.81)	0.033
Non-LBBB	11/17 (71.7%)	26/43 (75.3%)	1.21 (0.59–2.47)	
LV EDD				
<66 mm	16/76 (25.7%)	44/105 (47.2%)	0.49 (0.28–0.87)	0.605
≥66 mm	20/83 (26.8%)	40/98 (42.9%)	0.76 (0.45–1.27)	
Overall	37/160 (26.6%)	87/208 (45.5%)	0.58 (0.39–0.86)	0.006

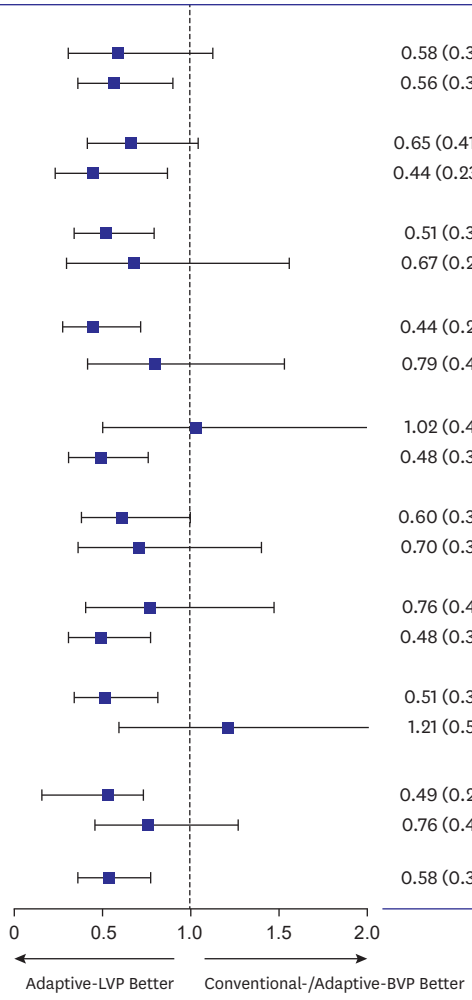

Figure 3. Forest plot of subgroup analyses for the primary outcome.
BMI = body mass index; BVP = biventricular pacing; EDD = end-diastolic diameter; ICMP = ischemic cardiomyopathy; LV = left ventricular; LVP = left ventricular pacing; NICMP = non-ischemic cardiomyopathy.

were excluded or re-classified according to their initial pacing configuration as in an intention-to-treat analysis (**Supplementary Figures 2** and **3**).

On multivariate Cox analysis, adaptive LVP, compared with BVP configurations, was identified as an independent protective factor of the primary composite outcome (HR, 0.58; 95% CI, 0.39–0.86; p=0.006) along with LBBB, QRS duration ≥150 ms, and the absence of paroxysmal AF (**Table 3**). To further validate these findings, additional multivariable models were constructed by incorporating more variables that are widely recognized as clinically relevant predictors of CRT response, including a non-parsimonious model. In all these additional analyses, adaptive LVP consistently demonstrated independent association with improved primary composite outcomes (**Supplementary Table 2**).

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Table 3. Predictors of the primary outcome

Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	p value	Hazard ratio	95% CI	p value
Age	1.00	0.99–1.02	0.678	1.00	0.99–1.02	0.984
Male	1.20	0.83–1.74	0.328	1.10	0.75–1.62	0.618
Height	1.01	0.99–1.03	0.328			
Body mass index	1.01	0.96–1.06	0.746			
Hypertension	1.01	0.71–1.44	0.950			
Diabetes	0.94	0.66–1.34	0.719			
Ischemic cardiomyopathy	1.67	1.10–2.53	0.016	1.21	0.76–1.92	0.427
Paroxysmal atrial fibrillation	2.18	1.45–3.27	<0.001	1.67	1.09–2.56	0.018
LBBB	0.35	0.24–0.51	<0.001	0.51	0.33–0.79	0.002
PR interval ≤200 msec	0.94	0.63–1.41	0.763			
QRS duration ≥150 msec	0.52	0.35–0.76	0.001	0.62	0.41–0.94	0.025
Adaptive LV pacing	0.53	0.36–0.77	0.001	0.58	0.39–0.86	0.006

CI = confidence interval; LBBB = left bundle branch block; LV = left ventricular.

DISCUSSION

This study represents the largest investigation of adaptive LVP or BVP versus conventional BVP in Asian HF patients (n=368), with a mean follow-up duration of 3.7 years—the longest reported to date for this population. The main findings of this study were as follows: 1) adaptive LVP was associated with a significantly lower risk of the primary clinical outcome than conventional BVP (HR, 0.56; 95% CI, 0.36–0.85; p=0.007), while adaptive BVP showed outcomes comparable to conventional BVP; 2) patients with a higher adaptive LVP percentage (>65%) had an even greater reduction in the risk of the primary composite outcome compared to conventional BVP; and 3) adaptive LVP consistently demonstrated superior clinical outcomes across various subgroups and remained an independent predictor of favorable long-term outcomes in multivariable analyses.

Compared with previous core CRT trials,[15-17] our data may better reflect the contemporary HF management using CRT devices, including a predominance of patients with LBBB morphology, optimal LV lead placement (mostly in non-apical LV lateral segment), and high CRT pacing percentages (**Table 1**). Mortality rates in this study were also comparable to those observed in the AdaptResponse study, the most recent CRT trial with the lowest mortality rates to date.[12] Furthermore, in patients meeting AdaptResponse criteria (PR interval ≤200 ms and LBBB morphology), our subgroup analysis revealed a further reduction in adverse clinical outcomes (**Supplementary Table 3**).

The adaptive LVP algorithm facilitates well-balanced ventricular activation by using LV-only stimulation (usually of LV lateral wall) synchronized with intrinsic RV/septal activation, which can minimize the potentially detrimental RV pacing burden, and eventually further improving long-term CRT outcomes.[18][19] Indeed, the advantages of adaptive LVP have already been noted in several previous hemodynamic and clinical studies. The maximum rate of LV pressure rise (i.e., LV dp/dt) was significantly higher in LVP synchronized with intrinsic RV activation than in BVP.[20-22] In the Adaptive CRT randomized trial, there was a lower risk of death or HFH (HR, 0.52; 95% CI, 0.27–0.98; p=0.044) with adaptive LVP than echo-optimized BVP in patients with normal AV conduction.[23] Mortality benefit of adaptive LVP was reproduced in the Personalized CRT Study, a real-world registry study comprising 1,841 patients.[8] Moreover, a higher adaptive LVP percentage was consistently associated with better outcomes.[1][4-6][10]

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However, previous aCRT studies mainly involved Western populations, typically including fewer than 50 Asian patients, and reported relatively short follow-up periods (<2 years).[7)9)11)] Thus, the applicability of these findings to Asian populations has been limited. Moreover, the most recent global randomized controlled trial (AdaptResponse) failed to demonstrate superiority of adaptive LVP over conventional BVP, contradicting the results from previous studies.[1)4-6)12)] Adaptive CRT demonstrated only a trend toward lower incidences of all-cause death or intervention for HF decompensation compared with conventional CRT (23.5% vs. 25.7% at 60 months, HR, 0.89; 95% CI, 0.78–1.01; p=0.077). In light of this context, we believe that the findings of the present study, involving a cohort entirely composed of Asian patients, hold significant implications for CRT therapy in Asian HF patients.

Several factors may explain the conflicting results between our study and AdaptResponse, although both study populations share similar patient characteristics, advanced pacing modulation, and relatively optimal use of HF medications (**Supplementary Table 3**). First, racial and ethnic differences were considerable, with more than 90% of AdaptResponse participants being from North America or Europe, while our cohort consisted entirely of Asian patients. Second, adaptive LVP appeared more beneficial in patients with smaller hearts. Subgroup analyses in our study revealed that certain characteristics suggesting smaller hearts,—including female sex, height <170 cm, BMI <25 kg/m^2, or LV end-diastolic diameter <66 mm—were associated with better outcomes (**Figure 3**). Similarly, in the AdaptResponse trial, the risk of the primary outcome tended to be lower in patients with QRS ≤150 ms compared to those with QRS >150 ms, and in the non-Western patients (including Asian patients) than those from a Western population. Finally, differences in the definition of the primary outcome may also have contributed to the discrepancies. Unlike AdaptResponse, which excluded appropriate ICD therapy from its primary composite outcome, our study included it. Given that adaptive LVP was associated with a reduced risk of ventricular arrhythmic events, its inclusion might have shifted the results in favor of adaptive LVP (**Supplementary Figure 4**).[24)]

Recent technological updates including novel CRT algorithms and conduction system pacing modes offer hope for further improvement in CRT outcomes. In a randomized study, left bundle branch (LBB) area pacing exhibited better performance than conventional BVP.[25-27)] Theoretically, combining the adaptive LVP algorithm with LBB pacing could emulate normal ventricular activation by synchronizing near-normal LV activation through LBB pacing with intrinsic normal RV activation. Future investigations should explore whether this approach can further enhance CRT efficacy. This study classified LBBB patients solely based on QRS morphology and duration without detailed characterization of underlying mechanisms such as the level of conduction block or the degree of LV fibrosis. This may contribute to patient heterogeneity, potentially limiting the clinical implications of our findings. Future CRT studies need to proceed in the direction of enhancing the predictive model using advanced diagnostics, such as cardiac magnetic resonance imaging and electrophysiologic studies, to incorporate additional predictors like myocardial fibrosis and conduction block level. Artificial intelligence-driven ECG or imaging analysis holds promise for providing individualized CRT management in this context.

This study had several limitations. First, it was a retrospective observational single-nation study. However, this is the largest real-world study to date to evaluate the effectiveness of aCRT in an Asian population. Although we conducted multivariate and various subgroup analyses, we cannot rule out that differences in baseline characteristics might have

affected outcomes. Second, interpretation of the results in patients with changes in pacing configuration is complicated. We did not exclude those patients given that this situation happens in real-world clinical setting; however, the main results were consistent whether those patients were excluded or re-classified according to their initial pacing configuration in the sensitivity analyses. Third, data on the burden of atrial high-rate episodes, which may influence the effectiveness of synchronized LV or BVP, were not collected in the initial case report form of this multicenter study. This limitation warrants further investigation in future studies. Fourthly, this study investigated the effectiveness of a specific adaptive CRT algorithm from a single manufacturer, which may limit the generalizability of our findings to other CRT devices. Lastly, we did not compare echocardiographic parameters indicative of structural remodeling due to the inherent limitation of retrospective study design. The number of echocardiographic exams, the timing of their assessment, and the measured values varied among centers. Echocardiographic parameters, such as LV volume, ejection fraction, and myocardial strain, could have provided additional insight, and therefore, further studies including standardized echocardiographic data are needed to elucidate the mechanistic basis of adaptive LV pacing.

The K-adaptive CRT study provided real-world evidence that adaptive LVP was associated with better clinical outcomes than conventional BVP in the Asian population. We suggest that Asian patients might benefit more from adaptive LVP than Western patients, and we advocate for special consideration of adaptive LVP in Asian HF patients.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1
Clinical outcomes in patients with left bundle branch block and PR ≤200 ms

Supplementary Table 2
Additional multivariate analysis models for predictors of the primary outcome

Supplementary Table 3
Comparison of baseline characteristics and clinical outcomes

Supplementary Figure 1
Kaplan-Meier estimates of time to primary outcome when including 12 patients who were excluded due to death, follow-up loss, or switched-off cardiac resynchronization therapy pacing within 3 months post-implant. The conventional BVP group was the reference.

Supplementary Figure 2
Kaplan-Meier estimates of time to primary outcome when excluding 34 patients with a reprogrammed pacing configuration.

Supplementary Figure 3
Kaplan-Meier estimates of time to primary outcome according to the initial pacing configuration.

Supplementary Figure 4
Incidence of appropriate implantable cardioverter-defibrillator therapy.

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