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Original Article
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Implantable Cardioverter-defibrillator Utilization and Its Outcomes in Korea: Data from Korean Acute Heart Failure Registry

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ABSTRACT

Background: There are sparse data on the utilization rate of implantable cardioverter-defibrillator (ICD) and its beneficial effects in Korean patients with heart failure with reduced left ventricular ejection fraction (LVEF).
Methods: Among 5,625 acute heart failure (AHF) patients from 10 tertiary university hospitals across Korea, 485 patients with reassessed LVEF ≤ 35% at least 3 months after the index admission were enrolled in this study. The ICD implantation during the follow-up was evaluated. Mortality was compared between patients with ICDs and age-, sex-, and follow-up duration matched control patients.
Results: Among 485 patients potentially indicated for an ICD for primary prevention, only 56 patients (11.5%) underwent ICD implantation during the follow-up. Patients with ICD showed a significantly lower all-cause mortality compared with their matched control population: adjusted hazard ratio (HR) (95% confidence interval [CI]) = 0.39 (0.16–0.92), $P = 0.032$. The mortality rate was still lower in the ICD group after excluding patients with cardiac resynchronization therapy (adjusted HR [95% CI] = 0.09 [0.01–0.63], $P = 0.015$). According to the subgroup analysis for ischemic heart failure, there was a significantly lower all-cause mortality in the ICD group than in the no-ICD group (HR [95% CI] = 0.20 [0.06–0.72], $P = 0.013$), with a borderline statistical significance (interaction $P = 0.069$).
Conclusion: Follow-up data of this large, multicenter registry suggests a significant under-utilization of ICD in Korean heart failure patients with reduced LVEF. Survival analysis implies that previously proven survival benefit of ICD in clinical trials could be extrapolated to Korean patients.

Trial Registration: ClinicalTrials.gov Identifier: NCT01389843

Keywords: Implantable Cardioverter-defibrillator; Heart Failure

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Disclosure
The authors have no potential conflicts of interest to disclosure

Author Contributions
Conceptualization: Choi DJ, Cho Y. Methodology: Choi DJ, Cho Y. Software: Cho Y, Cho SY. Validation: Oh IY, Lee JH, Park JJ, Choi DJ. Formal analysis: Cho Y, Cho SY. Investigation: Park JJ, Lee HY, Oh BH, Choi DJ. Data cruation: Park JJ, Lee HY, Kim KH, Yoo BS, Kang SM, Back SH, Jeon ES, Kim JJ, Cho MC, Chae SC, Oh BH, Choi DJ. Writing - original drafting: Cho Y, Cho SY. Writing - review & editing: Oh IY, Lee JH, Park JJ, Lee HY, Kim KH, Yoo BS, Kang SM, Back SH, Jeon ES, Kim JJ, Cho MC, Chae SC, Oh BH, Choi DJ.

INTRODUCTION

Sudden deaths are common among patients with heart failure with reduced ejection fraction (HFrEF), and electrical disturbances, such as ventricular tachycardia, bradycardia, and asystole, are considered as major contributors to HFrEF.[1] Implantable cardioverter-defibrillator (ICD) is an effective treatment for both bradycardia and potentially lethal ventricular arrhythmias and has proven its beneficial effects on the prevention of sudden cardiac deaths in patients with systolic dysfunction.[2,3] In the MADIT-II trial, ICD implantation reduced sudden arrhythmic death in patients with ischemic heart failure.[4] Moreover, it has been shown in the SCD-HeFT trial that ICD was better than medical treatment alone with respect to reducing mortality in patients with either ischemic or non-ischemic HFrEF.[5] Thus, contemporary guidelines recommend ICD to prevent sudden death in patients with symptomatic HF and left ventricular ejection fraction (LVEF) ≤ 35%, after a sufficient trial of optimal medications, including angiotensin-converting enzyme inhibitor (ACE-I) and beta-blockers.[6-10] Although several studies reported that the adherence to these guidelines improved the outcomes in Korean heart failure population,[11,12] to the best of our knowledge, there are sparse data on the status of ICD utilization and its outcomes in this population. Therefore, we sought to evaluate the utilization of ICDs and its mortality in Korean systolic heart failure patients using Korean prospective multicentre cohort study registry.

METHODS

Study population and Korean acute heart failure (KorAHF) registry

The KorAHF registry was a prospective, multicentre cohort study that enrolled patients hospitalized for acute heart failure (AHF) from 10 tertiary university hospitals throughout the country from March 2011 to December 2014. Detailed information on the study design and its results have been previously reported [ClinicalTrial.gov NCT01389843].[13] Patients with signs or symptoms of heart failure and either lung congestion, objective findings of left ventricular (LV) systolic dysfunction, or structural heart disease were eligible for the study. All patients were scheduled for follow-up at least 3 years after the index hospitalization.

Among the total of 5,625 patients with AHF enrolled in the KorAHF registry, those with the potential for primary prevention ICD implantation were enrolled in this study. Exclusion criteria were as follows: 1) patients who had an ICD implanted before or during the index admission, 2) patients who experienced sustained VT during index admission, 3) patients who lacked follow-up data on ICD implantation and echocardiography after being discharged from index admission. Because the current guidelines recommend optimal medical treatment for at least 3 months prior to ICD implantation,[2,3] patients showing reduced LVEF (≤ 35%) for at least 3 months after the index admission were considered eligible for enrolment in this study. A flow chart representing the selection of the study population in **Fig. 1**.

Follow-up and study endpoints

Patients' follow-up data were collected by the attending physician, with help of a clinical research coordinator, via a web-based system named the Clinical Data Management System (iCReaT) from the Korea National Institute of Health (NIH). Follow-up data were collected up to 60 months. Details for data collection protocol were described in previous studies.[13-15] The primary endpoint of the KorAHF registry was the all-cause mortality rate. For the purpose of this study, we investigated the rate of ICD implantation among those considered eligible

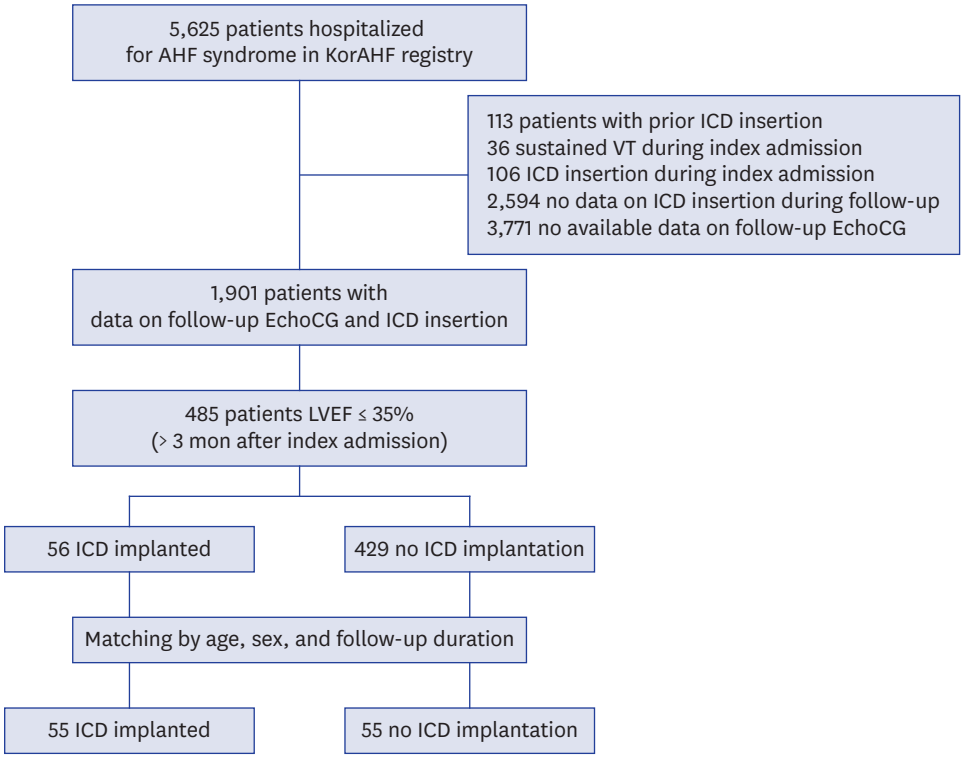

Fig. 1. Flowchart of the study population.
KorAHF = The Korean Acute Heart Failure registry, ICD = implantable cardioverter-defibrillator, EchoCG = echocardiography, LVEF = left ventricular ejection fraction.

for ICD implantation after the discharge from the index admission. And the post-discharge all-cause mortalities were compared between the patients with (ICD group) and without ICD implantation (no-ICD group).

Analysis in matched population

Additional matched analysis was performed to address the issue of selection bias. First, for each patient from the ICD group, age- (± 2 years tolerance) and sex-matched patients were screened from the no-ICD group. If the follow-up duration of the patient in the no-ICD group was shorter than the time to ICD insertion of the corresponding patient in the ICD group, the patient was excluded. Then individually matched control was randomly selected among these candidates in 1:1 ratio. One patient in the ICD group was excluded from this process due to the lack of matched patient with comparable follow-up duration.

Statistical analysis

Data are presented as the numbers and frequencies for categorical variables and as the means ± standard deviations for continuous variables. To make comparisons among groups, the χ^2 test (or Fisher's exact test) was used for categorical variables, and the unpaired Student's *t*-test (or Mann-Whitney U test) was used for continuous variables. Kaplan–Meier curves were plotted and compared, using the log-rank test for evaluation of post-discharge outcomes. A multivariable Cox proportional-hazards regression models were used to determine the independent effect of ICD insertion time on post-discharge outcomes, respectively. Variables found to be statistically significant ($P < 0.1$) in the univariate analysis were included in the multivariable model, except for variables with > 10% missing values or variables with a close

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association with other clinical variables. A two-sided probability value < 0.05 was considered significant. Statistical tests were performed using R programming version 3.6.0 (The R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org).

Ethics statement

The study protocol was approved by the Institutional Review Board (IRB) at each hospital and complied with the Declaration of Helsinki, and the requirement for written informed consent was waived (Seoul National University Bundang Hospital, IRB No. B-1104/125-014).

RESULT

Utilization of ICD in study population

Among the 485 patients whose follow-up echocardiography showed sustained reduced left ventricular systolic function (LVEF ≤ 35%), only 56 patients (11.5%) underwent ICD implantation during the follow-up. The median follow-up 1,046 days (interquartile range [IQR], 618–1,357 days), the median time to ICD implant was 539 days (IQR, 273–832). The median time to follow-up echocardiography from the index admission was 329 days (IQR, 211–413). Cardiac resynchronization therapy defibrillator (CRT-D) was used in 35.7% (20/56) of the ICD group, while CRT pacemaker (CRT-P) was used in only 0.2% (1/429) of the no-ICD group. The clinical characteristics according to the insertion of ICD during follow-up are provided in **Table 1**. Younger age (ICD vs. no ICD group; 62.9 ± 13.0 vs. 68.7 ± 13.9, $P = 0.003$), male sex (82.1% vs. 60.1%, $P = 0.002$), and more depressed LVEF (23.1 ± 7.7% vs. 27.9 ± 9.8%, $P < 0.001$) at the time

Table 1. Baseline characteristics and utilization of ICD

Characteristics	ICD implant (n = 56)	No ICD (n = 429)	*P* value
Age, yr	62.9 ± 13.0	68.7 ± 13.9	0.003
Male	46 (82.1)	258 (60.1)	0.002
BMI	24.7 ± 4.1	23.2 ± 3.6	0.003
Hypertension	29 (51.8)	252 (58.7)	0.397
Diabetes mellitus	31 (55.4)	195 (45.5)	0.210
Ischemic heart disease	20 (35.7)	176 (41.0)	0.537
Valvular heart disease	3 (5.4)	46 (10.7)	0.309
Cerebrovascular disease	10 (17.9)	54 (12.6)	0.376
Chronic kidney disease	6 (10.7)	82 (19.1)	0.177
Malignancy	3 (5.4)	36 (8.4)	0.600
COPD	3 (5.4)	48 (11.2)	0.269
De novo heart failure	27 (48.2)	165 (38.5)	0.208
AF	9 (16.1)	104 (24.2)	0.233
Previous HF admission	22 (39.3)	190 (44.3)	0.571
ICU admission	26 (46.4)	204 (47.0)	1.000
Mechanical ventilation	6 (10.7)	43 (10.0)	1.000
LVEF, %	23.1 ± 7.7	27.9 ± 9.8	< 0.001
LA dimension, mm	47.9 ± 5.6	48.4 ± 9.1	0.536
Hemoglobin, g/dL	13.6 ± 2.2	12.4 ± 2.2	< 0.001
Serum creatinine, mg/dL	1.5 ± 1.2	1.6 ± 1.6	0.466
Discharge medication			
ACEi or ARB, %	50 (89.3)	328 (76.5)	0.045
Beta-blocker, %	36 (64.3)	215 (50.1)	0.064
CRT	20 (35.7)	1 (0.2)	< 0.001
Time to f/u echocardiography	324 ± 120	321 ± 136	0.878

Data are expressed as mean ± standard deviation or number (%).
ICD = indicates implantable cardioverter-defibrillator, BMI = body mass index, COPD = chronic obstructive pulmonary disease, AF = atrial fibrillation, HF = heart failure, ICU = intensive care unit, LVEF = left ventricular ejection fraction, LA = left atrium, ACEi = angiotensin-converting-enzyme inhibitors, ARB = angiotensin receptor blocker, CRT = cardiac resynchronization therapy.

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of index admission were correlated with future ICD implantation. The prescription rate of beta-blocker or renin-angiotensin system inhibitor (RAS-inhibitor) at the time of discharge tended to be higher in patients who received ICD implantation (ICD vs. no-ICD group; 64.3% vs. 50.1%, $P = 0.064$ for beta-blocker, 89.3% vs. 76.5%, $P = 0.045$ for RAS-inhibitor). The etiology of heart failure and proportion of other comorbidities, such as hypertension, diabetes, cerebrovascular disease, and malignancy, were not different between groups.

Predictors for mortality during follow-up

The predictors for all-cause mortality were screened in the study population. These are presented in **Table 2**. ICD implantation was significantly correlated with favorable mortality outcome in univariate analysis, and also in multivariate analysis (**Table 2**). The hazard ratio was 0.30 (95% confidence interval [CI], 0.16–0.59; $P < 0.001$) and 0.43 (95% CI, 0.22–0.82; $P = 0.011$), before and after the adjustment for other variables, respectively. Older age, female sex, lower body mass index (BMI), hypertension, ischemic heart disease, chronic kidney disease, ADHF, previous history of HF admission, higher baseline LVEF, lower hemoglobin, higher serum creatinine level, no prescribed ACEi or ARB, and beta-blocker were also significantly correlated with the higher all-cause mortality in univariate analysis. In multivariate analysis, age, BMI, chronic kidney disease, previous HF admission, and no prescribed beta-blocker were significantly correlated with mortality.

Comparison of mortality in matched population

The baseline characteristics for the 1:1 matched population are presented in **Table 3**. All unmatched variables also became comparable between the ICD and no-ICD groups.

Table 2. Predictors for all-cause mortality

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
ICD insertion	0.32 (0.17–0.60)	< 0.001	0.43 (0.22–0.82)	0.011
CRT insertion	0.57 (0.25–1.29)	0.177		
Age	1.04 (1.03–1.05)	< 0.001	1.03 (1.01–1.04)	0.001
Male	0.74 (0.56–0.99)	0.043	1.05 (0.76–1.44)	0.758
BMI	0.93 (0.90–0.97)	0.001	0.95 (0.91–0.99)	0.022
Hypertension	1.63 (1.21–2.19)	0.001	1.23 (0.89–1.70)	0.201
Diabetes	1.26 (0.95–1.67)	0.110	1.24 (0.91–1.71)	0.179
Ischemic heart disease	1.35 (1.02–1.79)	0.038	0.91 (0.67–1.25)	0.567
Valvular heart disease	0.70 (0.41–1.18)	0.179		
COPD	1.51 (0.99–2.30)	0.056	1.13 (0.73–1.75)	0.577
Cerebrovascular disease	1.27 (0.86 –1.89)	0.227		
Chronic kidney disease	2.59 (1.90–3.52)	< 0.001	2.07 (1.39–3.08)	< 0.001
Malignancy	1.31 (0.80–2.12)	0.281		
ADHF (vs. de novo)	1.66 (1.22–2.25)	0.001	0.91 (0.57–1.45)	0.692
Previous HF admission	1.83 (1.38–2.44)	< 0.001	1.76 (1.15–2.68)	0.009
Atrial fibrillation	1.04 (0.75–1.46)	0.797		
LVEF	1.02 (1.00–1.03)	0.023	1.00 (0.98–1.02)	0.987
LA	1.01 (0.99–1.03)	0.237		
Hemoglobin	0.86 (0.81–0.92)	< 0.001	1.02 (0.91–1.06)	0.632
Creatinine	1.07 (1.01–1.13)	0.027	0.99 (0.88–1.11)	0.884
ICU admission	1.04 (0.79–1.39)	0.764		
Mechanical ventilation	1.29 (0.83–1.99)	0.255		
ACEi or ARB[a]	0.63 (0.46–0.87)	0.005	0.88 (0.63–1.23)	0.440
Beta-blocker[a]	0.50 (0.38–0.67)	< 0.001	0.56 (0.41–0.75)	< 0.001

HR = hazard ratio, CI = confidence interval, ICD = indicates implantable cardioverter-defibrillator, CRT = cardiac resynchronization therapy, BMI = body mass index, COPD = chronic obstructive pulmonary disease, ADHF = acute decompensated heart failure, HF = heart failure, LVEF = left ventricular ejection fraction, LA = left atrium, ICU = intensive care unit, ACEi = angiotensin-converting-enzyme inhibitors, ARB = angiotensin receptor blocker.
[a]Medications prescribed at discharge from index admission.

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Table 3. Baseline characteristics in matched population

Characteristics	Including CRT-D			Excluding CRT-D		
	ICD implant (n = 55)	No ICD (n = 55)	*P* value	ICD implant (n = 35)	No ICD (n = 35)	*P* value
Age, yr	63.0 ± 13.1	62.9 ± 12.9	0.965	60.1 ± 13.3	60.2 ± 13.1	0.957
Male	46 (83.6)	46 (83.6)	1.000	29 (82.9)	29 (82.9)	1.000
BMI	24.8 ± 4.1	24.7 ± 3.9	0.896	24.6 ± 4.0	23.6 ± 2.3	0.508
Hypertension	28 (50.9)	31 (56.4)	0.702	17 (48.6)	19 (54.3)	0.811
Diabetes mellitus	30 (54.5)	29 (52.7)	1.000	19 (54.3)	22 (62.9)	0.627
Ischemic heart disease	20 (36.4)	21 (38.2)	1.000	11 (31.4)	9 (25.7)	0.791
Valvular heart disease	3 (5.5)	4 (7.3)	1.000	2 (5.7)	3 (8.6)	1.000
Cerebrovascular disease	10 (18.2)	9 (16.4)	1.000	6 (17.1)	7 (20.0)	1.000
Chronic kidney disease	5 (9.1)	9 (16.4)	0.391	1 (2.9)	7 (20.0)	0.060
Malignancy	3 (5.5)	4 (7.3)	1.000	2 (5.7)	2 (5.7)	1.000
COPD	3 (5.5)	8 (14.5)	0.204	1 (2.9)	3 (8.6)	0.607
De novo heart failure	27 (49.1)	21 (38.2)	0.336	19 (54.3)	12 (34.3)	0.149
AF	9 (16.4)	16 (29.1)	0.172	9 (31.4)	11 (31.4)	0.791
Previous HF admission	22 (40.0)	25 (40.0)	0.700	12 (34.3)	15 (42.9)	0.623
ICU admission	26 (47.3)	29 (52.7)	0.703	16 (45.7)	19 (54.3)	0.633
Mechanical Ventilation	6 (10.9)	4 (7.3)	0.740	5 (14.3)	0 (0.0)	0.063
LVEF (baseline), %	22.8 ± 7.6	25.1 ± 9.3	0.181	21.8 ± 7.2	23.0 ± 9.0	0.524
LA dimension, mm	47.9 ± 5.7	50.1 ± 8.7	0.117	48.1 ± 5.5	50.2 ± 7.9	0.199
Hemoglobin, g/dL	13.7 ± 2.2	13.3 ± 2.6	0.415	13.9 ± 2.3	13.5 ± 2.7	0.477
Serum creatinine, mg/dL	1.4 ± 1.0	1.7 ± 1.2	0.193	1.2 ± 0.8	1.7 ± 1.3	0.038
Discharge medication						
ACEi or ARB, %	50 (90.9)	46 (83.6)	0.391	34 (97.1)	29 (82.9)	0.111
Beta-blocker, %	36 (65.5)	32 (58.2)	0.556	26 (74.3)	21 (60.0)	0.309
CRT	20 (36.4)	0 (0)	< 0.001	NA	NA	NA

Data are expressed as mean ± standard deviation or number (%).
CRT = cardiac resynchronization therapy, ICD = indicates implantable cardioverter-defibrillator, BMI = body mass index, COPD = chronic obstructive pulmonary disease, AF = atrial fibrillation, HF = heart failure, ICU = intensive care unit, LVEF = left ventricular ejection fraction, LA = left atrium, ACEi = angiotensin-converting-enzyme inhibitors, ARB = angiotensin receptor blocker.

Excluding the 20 CRT-D patients and their paired no-ICD group patients, the serum creatinine level was significantly correlated with ICD implantation during the follow-up period. The presence of chronic kidney disease and application of mechanical ventilation during the index admission also tended to be correlated with ICD insertion. After matching, Cox proportional survival analysis revealed that mortality was still significantly lower in the ICD group. HR was 0.45 (95% CI, 0.20–0.98; $P = 0.044$) and 0.39 (95% CI, 0.16–0.92; $P = 0.032$) before and after adjustment for other variables, respectively (**Table 4**). After excluding 20 CRT-D related pairs, the mortality rate was still lower in the ICD group compared with the no-ICD group before (HR [95% CI] = 0.30 [0.10–0.95], $P = 0.041$) and after adjustments (HR [95% CI] = 0.09 [0.01–0.63], $P = 0.015$). Kaplan-Meier estimates of survival in the overall and matched study population are shown in **Fig. 2**.

Subgroup analysis

We performed exploratory subgroup analysis in the matched study population. In the ischemic heart failure subgroup, the all-cause mortality rate during the follow-up period was significantly lower in the ICD insertion group than in the ICD non-insertion group (HR [95% CI] = 0.20 [0.06–0.72], $P = 0.013$), with a borderline interaction *P* value (interaction $P = 0.069$). Other than the etiology of HF, the effects of ICD insertion on mortality were not significantly different according to sex, diabetes mellitus, hypertension, chronic kidney disease, atrial fibrillation, or type of HF (**Table 5**).

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Table 4. Predictors for all-cause mortality in matched population

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
ICD insertion	0.45 (0.20–0.98)	0.044	0.39 (0.16–0.92)	0.032
CRT insertion	1.15 (0.46–2.84)	0.769		
Age	1.06 (1.02–1.10)	0.005	1.12 (1.04–1.20)	0.001
Male	0.36 (0.16–0.83)	0.016	0.54 (0.17–1.70)	0.290
BMI	0.91 (0.80–1.04)	0.149	0.95 (0.84–1.07)	0.381
Hypertension	1.16 (0.54–2.47)	0.708	2.95 (1.10–7.91)	0.031
Diabetes	1.91 (0.86–4.26)	0.115	1.52 (0.58–3.95)	0.392
Ischemic heart disease	1.79 (0.84–3.84)	0.132	0.86 (0.63–1.18)	0.358
Valvular heart disease	NA	NA		
COPD	3.04 (1.05–8.82)	0.041	2.82 (0.72–11.0)	0.136
Cerebrovascular disease	1.92 (0.77–4.77)	0.160		
Chronic kidney disease	3.12 (1.32–7.40)	0.010	1.49 (0.30–7.32)	0.622
Malignancy	0.56 (0.08–4.11)	0.566		
ADHF (vs. de novo)	2.32 (0.98–5.49)	0.056	2.21 (0.44–11.2)	0.338
Previous HF admission	2.14 (0.99–4.62)	0.052	1.71 (0.42–6.95)	0.454
Atrial fibrillation	0.91 (0.37–2.27)	0.841		
LVEF (baseline)	1.00 (0.96–1.04)	0.914	0.97 (0.92–1.02)	0.224
LA	1.02 (0.96–1.09)	0.440		
Hemoglobin	0.79 (0.67–0.92)	0.003	1.13 (0.93–1.36)	0.211
Creatinine	1.39 (1.07–1.80)	0.013	1.15 (0.69–1.91)	0.588
ICU admission	0.78 (0.36–1.67)	0.523		
Mechanical ventilation	1.92 (0.66–5.56)	0.229		
ACEi or ARB[a]	0.35 (0.14–0.88)	0.025	0.77 (0.23–2.52)	0.661
Beta-blocker[a]	0.49 (0.23–1.05)	0.066	0.30 (0.12–0.73)	0.008

HR = hazard ratio, CI = confidence interval, ICD = indicates implantable cardioverter-defibrillator, CRT = cardiac resynchronization therapy, BMI = body mass index, COPD = chronic obstructive pulmonary disease, ADHF = acute decompensated heart failure, HF = heart failure, LVEF = left ventricular ejection fraction, LA = left atrium, ICU = intensive care unit, ACEi = angiotensin-converting-enzyme inhibitors, ARB = angiotensin receptor blocker.
[a]Medications prescribed at discharge from index admission.

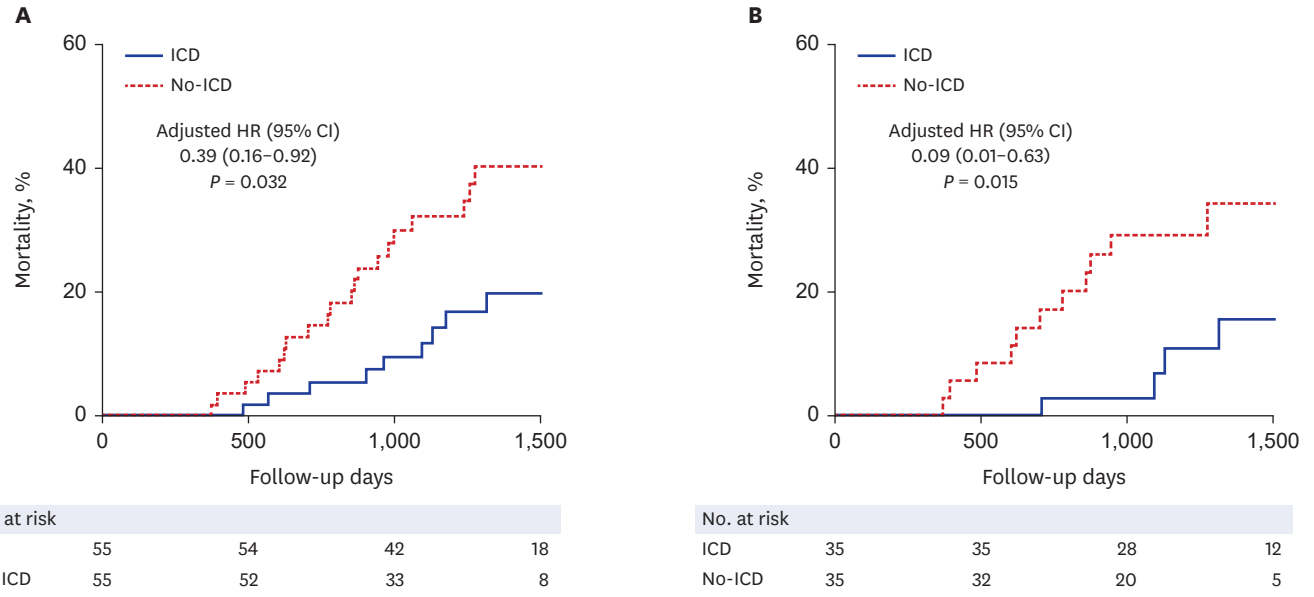

Fig. 2. All-cause mortality according to the ICD implantation during follow-up. (**A**) In the matched study population, and (**B**) after excluding patients with CRT-D and their matched controls.
ICD = implantable cardioverter-defibrillator, HR = hazard ratio, CI = confidence interval.

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Table 5. HRs for mortality with ICD insertion in subgroups of matched population

Variables	No. of patients	HR (95% CI)	*P* value	Interaction *P* value
Etiology of HF				0.069
Ischemic	41	0.20 (0.06–0.72)	0.013	
Non-ischemic	69	0.81 (0.29–2.29)	0.680	
Sex				0.785
Male	92	0.46 (0.19–1.08)	0.074	
Female	18	0.34 (0.06–1.74)	0.195	
Diabetes mellitus				0.897
Yes	56	0.40 (0.15–1.04)	0.059	
No	54	0.43 (0.11–1.76)	0.243	
Hypertension				0.300
Yes	58	0.67 (0.23–1.93)	0.455	
No	52	0.25 (0.08–0.84)	0.025	
Chronic kidney disease				0.209
Yes	14	1.09 (0.24–4.96)	0.914	
No	96	0.36 (0.15–0.87)	0.023	
Atrial fibrillation				0.719
Yes	28	0.30 (0.03–2.58)	0.273	
No	85	0.44 (0.19–1.01)	0.052	
Type of heart failure				0.271
De novo	48	0.22 (0.04–1.08)	0.062	
ADHF	62	0.60 (0.25–1.44)	0.251	

Hazard ratios for all-cause mortality associated with ICD implantation.
HR = hazard ratio, ICD = indicates implantable cardioverter-defibrillator, CI = confidence interval, HF = heart failure, ADHF = acute decompensated heart failure.

DISCUSSION

In patients with sustained LV dysfunction, ICD implantation is recommended for the improvement of survival. The aims of this study were 1) to speculate the utilization rate of ICDs in Korean heart failure patients and 2) to evaluate the efficacy of ICDs in Korean heart failure patients, using a prospective large multi-center KorAHF registry. Among the 5,625 KorAHF patients, there were 485 identifiable ICD candidates for primary prevention based on their follow-up transthoracic echocardiography. Among them, only 56 (11.5%) patients underwent ICD implantation, implying under-utilization of ICDs in Korean LV dysfunction heart failure patients. In the matched analysis, all-cause mortality was significantly lower in patients with ICD implantation than in patients without ICD implantation. This suggests that there is indeed a beneficial effect of ICD in patients with advanced HF. This is in line with previous randomized trials and their meta-analysis conducted in western countries,[16-18] which could be extrapolated to Korean patients.

There were several studies reporting the primary prevention ICD implantation rates in patients with advanced heart failure. The TRIUMPH registry data demonstrated that among the patients who survived myocardial infarction (MI) and had LVEF < 40% at discharge, only 35% underwent LVEF reassessment at 6 months and 2.4% received an ICD at 1 year.[19] More recently, Pokorney et al.[20] reviewed Medicare-insured patients with EF ≤ 35% during index myocardial infarction admission and reported that among those who underwent EF reassessment after discharge from the index admission, only 11% received an ICD within 1 year. In the Swedish Heart Failure Registry, ICD for primary prevention was also underused (ICD implantation rate 9.6%).[21] Percent of LVEF improvement was not presented in these two papers. There was a recent report on the increasing annual number of ICD implantation in Korea, but the utilization rates among eligible population was not considered in this paper.[22] The current study showed that the ICD implantation rate in Korean heart failure

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patients eligible for primary prevention ICD was about 11.5% during the overall follow-up. The ICD insertion rate at 1-year follow-up was lower than this, which was 6.6%. The ICD insertion rate in real-world practice might be even lower, considering that the KorAHF only enrolled patients from 10 major tertiary hospitals in Korea. In addition, it should be considered that our study only enrolled patients who were considered eligible for an ICD. Eligibility for an ICD was based on the echocardiographic results, at least 3 months apart from the index admission. Optimal medical treatment was assumed during this period, because the hospitals participating in this KorAHF study were tertiary hospitals with cardiologists specialized in heart failure treatment. In the subgroup of patients who were prescribed both RAS inhibitors and beta-blockers at discharge, ICD insertion rates were 9.1% at 1-year follow-up and 16.7% during overall follow-up, still demonstrating low utilization of ICDs. The low rate of ICD utilization can be attributed to factors from both patients and physicians. In this study, young age, male sex, and higher BMI were correlated with future ICD implantation. Other than underlying diseases, financial status, physicians' attitude and patients' preference for ICDs may have also influenced the utilization of ICD, although such data were not available. Several previous studies suggested that there may be a correlation between regional supply of cardiologists or electrophysiologists and ICD usage.[23-25] However, at least for our study, such correlation was not the cause of low ICD usage, because hospitals participating in KorAHF were all tertiary hospitals with a plethora of qualified cardiologists and electrophysiologists. Referral to an ICD interventionist may be another hindering step. Gupta et al.[26] demonstrated that electronic medical record based reminders improved both ICD discussion rate (44% to 67%) and implantation rate (2% to 24%), suggesting that improvement in this referring step can make a real difference in the utilization of ICD.

The beneficial effects of ICDs in patients with advanced systolic heart failure have not sufficiently been addressed in Asian patients, especially in Korean patients.[4,5,16-18] Although there have been a few studies involving Korean patients with respect to ICD implantation,[27-30] they present the outcomes in a single-arm observational environment, without any comparison to a control population. The present study enrolled patients with long-lasting systolic heart failure with ICD implantation and compared them against their match patients without ICD implantation. To the best of our knowledge, this is the first study demonstrating the benefits of ICDs in Korean patients with systolic heart failure. In the SCD-HeFT study, the benefit of ICD on the prevention of mortality was shown in patients with systolic heart failure, either ischemic or non-ischemic.[5] However, a recent DANISH trial raised questions about the usefulness of ICD in non-ischemic cardiomyopathy.[31] The subgroup analysis of the present study also demonstrated a trend of differential benefits of ICD according to the etiology of HF. The mortality of the ICD group was significantly lower than that of the control group in the ischemic HF subgroup (HR [95% CI] = 0.20 [0.06–0.72], P = 0.013), while the mortalities were comparable between the groups in the non-ischemic HF subgroup (HR [95% CI] = 0.81 [0.29–2.29], P = 0.680). Interaction P value was borderline (0.069). (**Table 5**) The benefits of ICD in patients receiving CRT have recently been questioned.[32] To address the confounding effect of CRT, additional survival analysis was performed after excluding CRT-D patients and their paired control patients. The mortality was still lower in the ICD group than in the control group (**Fig. 2B**), suggesting that there is a clear beneficial effect of ICDs in the study population.

This study has several limitations. This is a prospective cohort study and there could be unaddressed biases such as sarcopenia in comparing the outcomes between the ICD and control groups. However, randomized trials there should be ethical issues in conduction randomized trials that evaluate the benefits of ICDs in this population. The matching process

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was adopted in this study in efforts to address this issue to some degree, though matching variables were limited due to the small number of the eligible patients. At least, there was no significant difference between the matched groups regarding the baseline characteristics including discharge medications. Information on prescription of the new drugs such as angiotensin receptor-neprilysin inhibitor or sodium-glucose cotransporter-2 inhibitor was not collected in the KorAHF registry. Mortality data were collected with assistance from the National Death Records, and survival analysis on specific cause of death, such as sudden cardiac death, was not feasible. After narrowing down the study population, the size of the matched population was rather underpowered to validate the effects of ICD in various subgroups. It was not possible to clarify the reasons for the low ICD utilization in this study.

In conclusion, follow-up data of this large multicenter KorAHF registry suggests a significant under-utilization of ICD in Korean heart failure patients with reduced LVEF. Survival analysis implies that benefits of ICD proven in clinical trials from western countries could be extrapolated to Korean patients.

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