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Risk of Atrial Fibrillation and Adverse Outcomes in Patients With Cardiac Implantable Electronic Devices

So-Ryoung Lee, MD, PhD[1,2,*], Ji Hyun Lee, MD, PhD[3,*], Eue-Keun Choi, MD, PhD[1,2], Eun-Kyung Jung, BS[4], So-Jeong You, BS[4], Seil Oh, MD, PhD[1,2], and Gregory YH Lip, MD[1,5,6]

[1]Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea
[2]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea
[3]Department of Cardiology, Cardiovascular Center, Seoul National University Bundang Hospital, Seongnam, Korea
[4]Medtronic Korea, Ltd., Seoul, Korea
[5]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Chest and Heart Hospital, Liverpool, United Kingdom
[6]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

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Correspondence to
Eue-Keun Choi, MD, PhD
Department of Internal Medicine, Seoul National University Hospital, 101, Daehak-ro, Jongno-gu, Seoul 03080, Korea.
Email: choiek17@snu.ac.kr

*So-Ryoung Lee and Ji Hyun Lee contributed equally to this work.

ORCID iDs
So-Ryoung Lee
https://orcid.org/0000-0002-6351-5015
Ji Hyun Lee
https://orcid.org/0000-0002-7162-1248
Eue-Keun Choi
https://orcid.org/0000-0002-0411-6372
So-Jeong You
https://orcid.org/0000-0002-3760-943X
Seil Oh
https://orcid.org/0000-0002-2504-9615
Gregory YH Lip
https://orcid.org/0000-0002-7566-1626

AUTHOR'S SUMMARY

Annually, 4 of 100 patients with pacemaker, 7 of 100 patients with implantable cardioverter-defibrillator/cardiac resynchronization therapy with heart failure, and 5 of 100 patients with implantable cardioverter-defibrillator without heart failure have been diagnosed with new-onset atrial fibrillation (AF) during follow-up. Common risk factors were older age and valvular heart disease across the three cardiac implantable electronic device (CIED) cohorts. AF significantly increased the risk of major cardiovascular adverse events. Risk stratification for the early detection of AF and integrated care for incident AF should be implemented to improve the clinical outcomes in patients with CIED.

ABSTRACT

Background and Objectives: Comprehensive epidemiological data are lacking on the incident atrial fibrillation (AF) in patients with cardiac implantable electronic devices (CIEDs). This study aimed to examine the incidence, risk factors, and AF-related adverse outcomes of patients with CIEDs.
Methods: This was an observational cohort study that analyzed patients without prevalent AF who underwent CIED implantation in 2009–2018 using a Korean nationwide claims database. The subjects were divided into three groups by CIED type and indication: pacemaker (n=21,438), implantable cardioverter defibrillator (ICD)/cardiac resynchronization therapy (CRT) with heart failure (HF) (n=3,450), and ICD for secondary prevention without HF (n=2,146). The incidence of AF, AF-associated predictors, and adverse outcomes were evaluated.
Results: During follow-up, the incidence of AF was 4.3, 7.3, and 5.1 per 100 person-years in the pacemaker, ICD/CRT with HF, and ICD without HF cohorts, respectively. Across the three cohorts, older age and valvular heart disease were commonly associated with incident AF. Incident AF was consistently associated with an increased risk of ischemic stroke (3.8–11.4-fold), admission for HF (2.6–10.5-fold), hospitalization for any cause (2.4–2.7-fold), all-cause death (4.1–5.0-fold), and composite outcomes (3.4–5.7-fold). Oral anticoagulation rates were

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Conflict of Interest

Eue-Keun Choi reported research grants or speaking fees from Bayer, BMS/Pfizer, Biosense Webster, Chong Kun Dang, Daiichi-Sankyo, Dreamtech Co., Ltd., Medtronic, Samjinpharm, Sanofi-Aventis, Seers Technology, Skylabs, and Yuhan.
Gregory YH Lip reports that he contributed consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo, but no fees are received personally; no other relationships or activities that could appear to have influenced the submitted work.
The other 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: Lee SR, Choi EK; Data curation: Lee SR; Formal analysis: Jung EK, You SJ; Funding acquisition: Choi EK; Investigation: Lee SR, Lee JH, Choi EK, You SJ; Methodology: Lee SR, Jung EK, You SJ; Project administration: Lee SR, Choi EK; Resources: Jung EK; Supervision: Choi EK, Oh S, Lip GYH; Validation: Lee SR, Lee JH; Visualization: Lee SR; Writing - original draft: Lee SR; Writing - review & editing: Lee JH, Choi EK, Oh S, Lip GYH.

suboptimal in patients with incident AF (pacemaker, 51.3%; ICD/CRT with HF, 51.7%; and ICD without HF, 33.8%, respectively).
Conclusions: A substantial proportion of patients implanted CIED developed newly diagnosed AF. Incident AF was associated with a higher risk of adverse events. The importance of awareness, early detection, and appropriate management of AF in patients with CIED should be emphasized.

Keywords: Atrial fibrillation; Pacemaker; Implantable cardioverter defibrillator; Cardiac resynchronization therapy; Risk factor

INTRODUCTION

The implantation of cardiac implantable electronic devices (CIEDs), including pacemakers, implantable cardioverter defibrillators (ICD), and cardiac resynchronization therapy (CRT) devices, has markedly increased in the recent decade for several reasons, including the increasing aging population and increasing overall burden of cardiovascular comorbidities.[1)2)] Notably, the prevalence of atrial fibrillation (AF) among patients who have undergone CIED implantation has also increased significantly.[2)]

In patients with CIED, special consideration is needed with regard to the detection and management of both prevalent and incident AF. First, CIED enhances the ability to identify incident AF. Second, individuals with CIED already have structural heart diseases such as heart failure (HF), or various types of heart rhythm disorders. Third, AF is associated with increased risks of stroke, aggravating HF, cardiovascular death, and all-cause death.[3)] The clinical impact of AF is likely to be more profound in patients with CIED who already have various degrees of structural heart diseases and heart rhythm disorders; in other words, a high-risk population. Finally, incident paroxysmal AF may be associated with a higher risk of inappropriate shock in patients with ICD and a higher risk of insufficient CRT delivery.[4)5)] Regarding these special considerations, the incidence of AF after CIED implantation, risk factors associated with incident AF, and the clinical impact of incident AF among patients who have undergone CIED implantation might be distinct from those of the general population. However, comprehensive epidemiological data are lacking on incident AF and its impact on outcomes in patients with CIED.

Therefore, here we aimed to evaluate the incidence of AF in patients with CIED and identify the risk factors associated with incident AF in this population using a nationwide population-based cohort. Second, we investigated the clinical impact of incident AF on the risk of AF-related adverse outcomes in patients with CIED.

METHODS

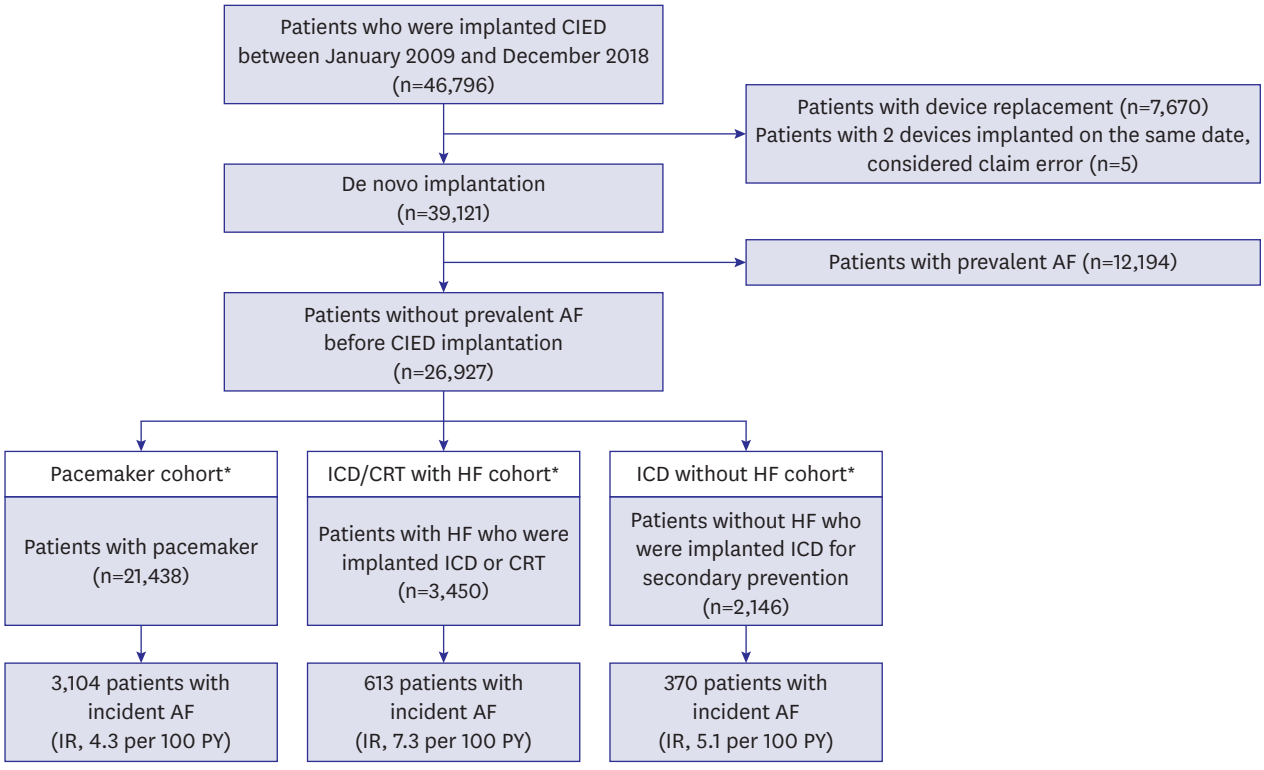
Ethical statement

This study complied with the Declaration of Helsinki (the latest version, 2013) and this study was exempted from review by the Institutional Review Board of Seoul National University Hospital (H-1802-080-923).

Data source and study population

The analyses were performed using the Korean National Health Insurance Service (NHIS) database. In South Korea, all citizens are mandatorily included in the NHIS system operated by the government.[6] The Korean NHIS, as a single insurer, provides comprehensive coverage for enrollees' medical use. Thus, the Korean NHIS database contains demographic information, and all medical expense claim data for the entire Korean population. The NHIS database includes subjects' demographic information; their International Classification of Disease, 10th Revision, Clinical Modification (ICD-10-CM) diagnostic codes; examinations; procedures; operations; and medical prescription records for outpatient and inpatient services.[6]

The study population enrollment flowchart is presented in **Figure 1**. We identified patients who had undergone CIED implantation between January 1, 2009, and December 31, 2018 (n=46,796). The detailed device codes of the CIED, including pacemakers, ICDs, and CRTs, are presented in **Supplementary Table 1**.[3] After excluding patients who required device replacement and those for whom two devices were claimed on the same date, 39,121 patients were identified. Patients with prevalent AF (ICD-10-CM code I48) during a 2-year screening period before the index CIED implantation were excluded (n=26,927).[3] We divided the subjects into 3 groups: patients with a pacemaker (pacemaker cohort), those with an ICD or CRT with HF (ICD/CRT with HF cohort), and those without HF who had undergone ICD implantation for secondary prevention (ICD without HF cohort). The definitions of ICD



*Same patients within 2 different cohort are considered independent cases for each cohort.
The numbers of duplicates between cohorts were 75 cases for pacemaker cohort, 4 cases for ICD/CRT with HF cohort, and 4 cases for ICD without HF cohort.

Figure 1. Study enrollment flow.
AF = atrial fibrillation; CIED = cardiac implantable electronic device; CRT = cardiac resynchronization therapy; HF = heart failure; ICD = implantable cardioverter defibrillator; IR = incidence rate; PY = person-years.

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for secondary prevention due to aborted sudden cardiac death (SCD), sustained ventricular tachycardia (VT), or ventricular fibrillation (VF) are presented in **Supplementary Table 1**.[3]

Covariates

Patients' age, sex, and comorbidities were obtained (**Supplementary Data 1**). Detailed operational definitions of comorbidities are presented in **Supplementary Table 1**.[3]

For the pacemaker cohort, device indication was classified into sick sinus syndrome (SSS, I495) or atrioventricular block (AVB; I441, I442, or I443). For ICD, secondary prevention was defined as the presence of relevant diagnostic codes, including aborted SCD (I460 or I469), sustained VT (I472), or VF (I490). Device types including single/dual chambers, CRT with a defibrillator (CRT-D)/CRT or with a pacemaker (CRT-P), were also described.

Study outcomes and follow-up

Incident atrial fibrillation

New-onset AF was identified from the index date of CIED implantation. Incident AF was defined based on the diagnostic code (I48) during admission or attendance at the outpatient clinic during follow-up.[7] Study populations were followed up until the incidence of AF, death, or the end of the study period (December 31, 2018), whichever came first.

Atrial fibrillation-related adverse outcomes

To evaluate the risk of AF-related adverse outcomes between patients with and without incident AF during follow-up, we updated the subjects' age and comorbidities at the time of AF diagnosis in patients with incident AF and matched them to those without incident AF by age and sex. After 3:1 or 2:1 matching of patients without incident AF versus those with incident AF in each CIED cohort, we identified the incidence of AF-related adverse outcomes including ischemic stroke, admission for HF, hospitalization for any cause, all-cause death, and composite outcome of ischemic stroke, admission for HF, and all-cause death. Detailed definitions of AF-related adverse outcomes are presented in **Supplementary Table 1**.[8] The index date of patients with incident AF was at least 7 days after the AF diagnosis. Patients were followed up until the occurrence of each adverse outcome, death, or the end of the study period (December 31, 2018), whichever came first.

We also identified the prescription of oral anticoagulants (OACs), consisting of warfarin or direct oral anticoagulants (DOACs) within a 1-year period after the AF diagnosis.

Statistical analysis

Categorical variables are presented as numbers and percentages. Continuous variables are presented as means with standard deviations or medians with interquartile ranges. Categorical variables were compared using the chi-square test (or Fisher's exact test, if applicable), while continuous variables were compared using the Student's t-test. The incidence rate (IR) of AF was estimated using the number of events during the total follow-up period divided by 100 person-years (PYs) at risk. The cumulative incidence of AF in each CIED cohort was analyzed using Kaplan-Meier curves.

To evaluate factors associated with incident AF, Cox regression analyses were performed for each CIED cohort. First, a univariable Cox regression analysis was executed for age (per 10 years), sex (women), comorbidities, and device indications/types, and a multivariable Cox regression analysis was performed on variables which had achieved a significance of $p<0.1$

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in the univariable Cox analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) are presented for the risk of incident AF for each variable.

To evaluate the risk of AF-related adverse outcomes using age- and sex-matched patients, one patient with incident AF was matched with three patients without incident AF in the pacemaker and ICD without HF cohorts, while one patient with incident AF was matched with two patients without incident AF in the ICD/CRT with HF cohort. After matching, the absolute standardized difference (ASD) was measured for all the variables to evaluate the balance of baseline characteristics between patients with and without incident AF. An ASD of ≤0.1 indicates a negligible intergroup difference.[9] The IR of each AF-related adverse outcome was estimated in the matched cohort using the number of events during the total follow-up period divided by 100 PYs at risk. A multivariable Cox regression analysis was used to calculate the risk of AF-related adverse outcomes after adjustment for age, sex, comorbidities, and/or the CHA_2DS_2-VASc score, if there was a significant intergroup difference (ASD >0.1). HRs and 95% CIs are presented for the risk of AF-related adverse outcomes in patients with incident AF versus those without incident AF (reference group).

Statistical significance was set at $p<0.05$. All statistical analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC, USA).

RESULTS

The baseline characteristics of each cohort are shown in **Table 1**. Finally, 21,438, 3,450, and 2,146 patients were included in the pacemaker, ICD/CRT with HF, and ICD without HF cohorts, respectively (**Figure 1**). The pacemaker cohort included the oldest population, followed by the ICD/CRT with HF cohort, while the ICD without HF cohort mainly included young and middle-aged adults (**Supplementary Figure 1**). Baseline characteristics according to incident AF in each CIED cohort are presented in **Table 1** and **Supplementary Data 2**.

Atrial fibrillation incidence and factors associated with incident atrial fibrillation in 3 cardiac implantable electronic device cohorts

The cumulative incidence curves for new-onset AF in each cohort are shown in **Figure 2**.

Pacemaker cohort

During the mean 41.1±32.7 months of follow-up, 3,104 patients were diagnosed with AF (crude IR, 4.3 per 100 PY). The HRs for incident AF among the pacemaker cohorts are presented in **Supplementary Table 2** and **Figure 3A**. After multivariable adjustment, SSS and valvular heart disease (VHD) were significantly associated with a higher risk of incident AF by 2.5-fold and 2.2-fold, respectively, in the pacemaker cohort. In addition, older age (per 10 years), prior ischemic stroke/transient ischemic attack (TIA), HF, hypertension, and women were associated with a higher risk of AF by 25%, 24%, 21%, 12%, and 4%, respectively.

Implantable cardioverter defibrillator/cardiac resynchronization therapy with heart failure cohort

During the mean 29.5±26.7 months of follow-up, 613 patients were diagnosed with AF (crude IR, 7.3 per 100 PY). After multivariable adjustment, VHD, prior ischemic stroke/TIA, and older age (per 10 years) were associated with a higher risk of AF by 1.9-fold. 1.3-fold, and 1.3-fold, respectively (**Supplementary Table 3**, **Figure 3B**).

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Table 1. Baseline characteristics of three cohorts according to the incidence of atrial fibrillation

	Pacemaker cohort				ICD/CRT with HF cohort				ICD without HF cohort			
	Total	Incident AF		p value	Total	Incident AF		p value	Total	Incident AF		p value
		No	Yes			No	Yes			No	Yes	
No.	21,438	18,334	3,104		3,450	2,837	613		2,146	1,776	370	
Age (year)												
Mean ± SD	71.5±12.1	71.6±12.1	70.9±11.6	0.001	62.2±13.4	62.2±13.5	62.4±13.1	0.798	50.3±15.4	49.4±15.4	54.5±14.4	<0.001
Female	12,835 (59.9)	11,032 (60.2)	1,803 (58.1)	0.028	1,141 (33.1)	951 (33.5)	190 (31.0)	0.228	470 (21.9)	399 (22.5)	71 (19.2)	0.165
CHA_2DS_2-VASc												
Mean ± SD	3.9±1.8	3.9±1.8	3.9±1.8	0.305	3.7±1.7	3.7±1.6	3.7±1.7	0.500	1.6±1.5	1.6±1.5	2.0±1.5	<0.001
Median (IQR)	4.0 (2.0)	4.0 (2.0)	4.0 (2.0)	0.486	4.0 (2.0)	4.0 (2.0)	4.0 (2.0)	0.725	1.0 (2.0)	1.0 (2.0)	2.0 (2.0)	<0.001
Comorbidities												
Hypertension	16,964 (79.1)	14,471 (78.9)	2,493 (80.3)	0.078	2,900 (84.1)	2,374 (83.7)	526 (85.8)	0.191	1,111 (51.8)	883 (49.7)	228 (61.6)	<0.001
DM	9,796 (45.7)	8,398 (45.8)	1,398 (45.0)	0.427	1,697 (49.2)	1,380 (48.6)	317 (51.7)	0.168	549 (25.6)	416 (23.4)	133 (35.9)	<0.001
HF	4,857 (22.7)	4,134 (22.5)	723 (23.3)	0.359	3,450 (100)	2,837 (100)	613 (100)	1.000	0 (0)	0 (0)	0 (0)	1.000
IS/TIA	3,793 (17.7)	3,117 (17.0)	676 (21.8)	<0.001	337 (9.8)	261 (9.2)	76 (12.4)	0.015	177 (8.2)	143 (8.1)	34 (9.2)	0.469
ICH	327 (1.5)	271 (1.5)	56 (1.8)	0.170	25 (0.7)	21 (0.7)	4 (0.7)	1.000	26 (1.2)	25 (1.4)	1 (0.3)	0.070
CAD	9,638 (45.0)	8,164 (44.5)	1,474 (47.5)	0.002	2,400 (69.6)	1,989 (70.1)	411 (67.0)	0.135	957 (44.6)	767 (43.2)	190 (51.4)	0.004
Prior MI	1,077 (5.0)	934 (5.1)	143 (4.6)	0.250	684 (19.8)	582 (20.5)	102 (16.6)	0.029	332 (15.5)	262 (14.8)	70 (18.9)	0.043
PAD	4,462 (20.8)	3,821 (20.8)	641 (20.7)	0.809	458 (13.3)	379 (13.4)	79 (12.9)	0.754	162 (7.5)	124 (7.0)	38 (10.3)	0.029
VHD	350 (1.6)	257 (1.4)	93 (3.0)	<0.001	61 (1.8)	43 (1.5)	18 (2.9)	0.016	16 (0.7)	9 (0.5)	7 (1.9)	0.012
Device indication				<0.001								
SSS	5,812 (27.1)	4,404 (24.0)	1,408 (45.4)									
AVB	14,751 (68.8)	13,234 (72.2)	1,517 (48.9)									
Device type and indication												
ICD					2,236 (64.8)	1,822 (64.2)	414 (67.5)		2,146 (100)	1,776 (100)	370 (100)	
Primary*					1,232 (35.7)	1,018 (35.9)	214 (34.9)		0 (0)	0 (0)	0 (0)	
Secondary*					1,004 (29.1)	804 (28.3)	200 (32.6)		2,146 (100)	1,776 (100)	370 (100)	
Aborted SCD					196 (5.7)	158 (5.6)	38 (6.2)		693 (32.3)	589 (33.2)	104 (28.1)	
Sustained VT					562 (16.3)	443 (15.6)	119 (19.4)		626 (29.2)	488 (27.5)	138 (37.3)	
VF					246 (7.1)	203 (7.2)	43 (7.0)		827 (38.5)	699 (39.4)	128 (34.6)	
CRT					1,214 (35.2)	1,015 (35.8)	199 (32.5)					
CRT-D					1,106 (32.1)	920 (32.4)	186 (30.3)					
CRT-P					108 (3.1)	95 (3.3)	13 (2.1)					
Chamber				<0.001				0.773				<0.001
Single	2,018 (9.4)	1,483 (8.1)	535 (17.2)		1,329 (38.5)	1,096 (38.6)	233 (38.0)		1,349 (62.9)	1,150 (64.8)	199 (53.8)	
Dual	19,420 (90.6)	16,851 (91.9)	2,569 (82.8)		2,121 (61.5)	1,741 (61.4)	380 (62.0)		797 (37.1)	626 (35.2)	171 (46.2)	

AF = atrial fibrillation; AVB = atrioventricular block; CAD = coronary artery disease; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronized therapy with pacemaker; DM = diabetes mellitus; HF = heart failure; ICD = implantable cardioverter defibrillator; ICH = intracranial hemorrhage; IS = ischemic stroke; MI = myocardial infarction; PAD = peripheral artery disease; SCD = sudden cardiac death; SSS = sick sinus syndrome; TIA = transient ischemic attack; VF = ventricular fibrillation; VHD = valvular heart disease; VT = ventricular tachycardia.
*Primary and secondary indicate the indication of ICD implantation: primary prevention and secondary prevention for SCD.

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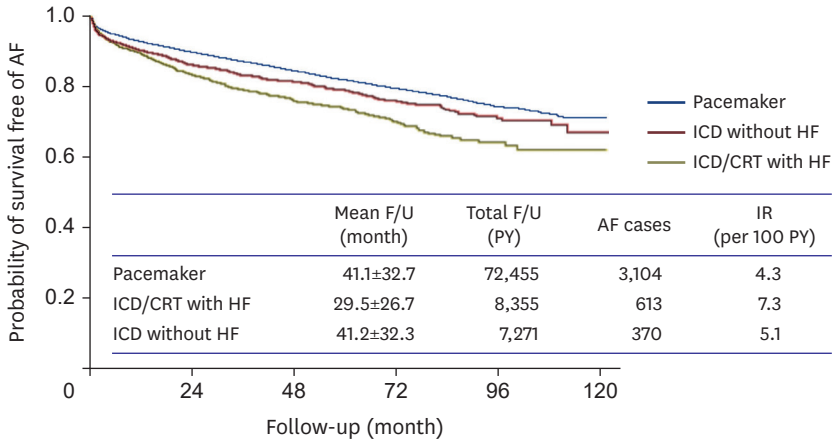

	Mean F/U (month)	Total F/U (PY)	AF cases	IR (per 100 PY)
Pacemaker	41.1±32.7	72,455	3,104	4.3
ICD/CRT with HF	29.5±26.7	8,355	613	7.3
ICD without HF	41.2±32.3	7,271	370	5.1

Number at risk						
Pacemaker	20,563	12,498	7,538	4,034	1,628	57
ICD/CRT with HF	3,450	1,575	741	304	89	1
ICD without HF	2,146	1,297	794	407	156	2

Figure 2. AF-free survival curves in each cohort.
AF = atrial fibrillation; CRT = cardiac resynchronization therapy; F/U = follow-up; HF = heart failure; ICD = implantable cardioverter defibrillator; IR = incidence rate; PY = person-years.

Implantable cardioverter defibrillator without heart failure cohort

During the mean 41.2±32.3 months of follow-up, 370 patients were diagnosed with AF (crude IR, 5.1 per 100 PY). VHD, diabetes mellitus, and older age (per 10 years) were associated with a higher risk of AF by 3.9-, 1.5-, and 1.2-fold, respectively (**Supplementary Table 4**, **Figure 3C**).

Atrial fibrillation-related adverse outcomes

The baseline characteristics of age- and sex-matched cohort are presented in **Supplementary Tables 5**, **6**, and **7** for each device cohort. Age, sex, and CHA_2DS_2-VASc score were well balanced with ASD ≤0.1. Patients with incident AF showed significantly higher crude IRs for all adverse outcomes than those without incident AF in all cohorts (**Figure 4**). After multivariable adjustment, although there were some differences in HRs among different cohorts, incident AF was consistently associated with an increased risk of ischemic stroke (3.8–11.4-fold), admission for HF (2.6–10.5-fold), hospitalization for any cause (2.4–2.7-fold), all-cause death (4.1–5.0-fold), and composite outcomes (3.4–5.7-fold) (**Figure 5**).

Oral anticoagulant prescription rate within 1 year after a new atrial fibrillation diagnosis

In the pacemaker cohort, 51.3% of patients (n=1,594) were initiated on OAC within 1 year after a new AF diagnosis; 17.9% were prescribed warfarin and 33.4% were prescribed DOACs. In the ICD/CRT with HF cohort, 51.7% of patients (n=315) were initiated on OACs: 23.6% on warfarin and 28.1% on DOACs. Among the ICD without HF cohort, 33.8% of patients (n=125) started OACs, 15.9% started warfarin, and 17.9% started DOACs. In patients with a CHA_2DS_2-VASc score ≥2 (70.3% of the pacemaker cohort, 89.7% of the ICD/CRT with HF cohort, and 56.5% of the ICD without HF cohort), 53.0%, 52.4%, and 42.1% were prescribed OACs within 1 year after the AF diagnosis, respectively.

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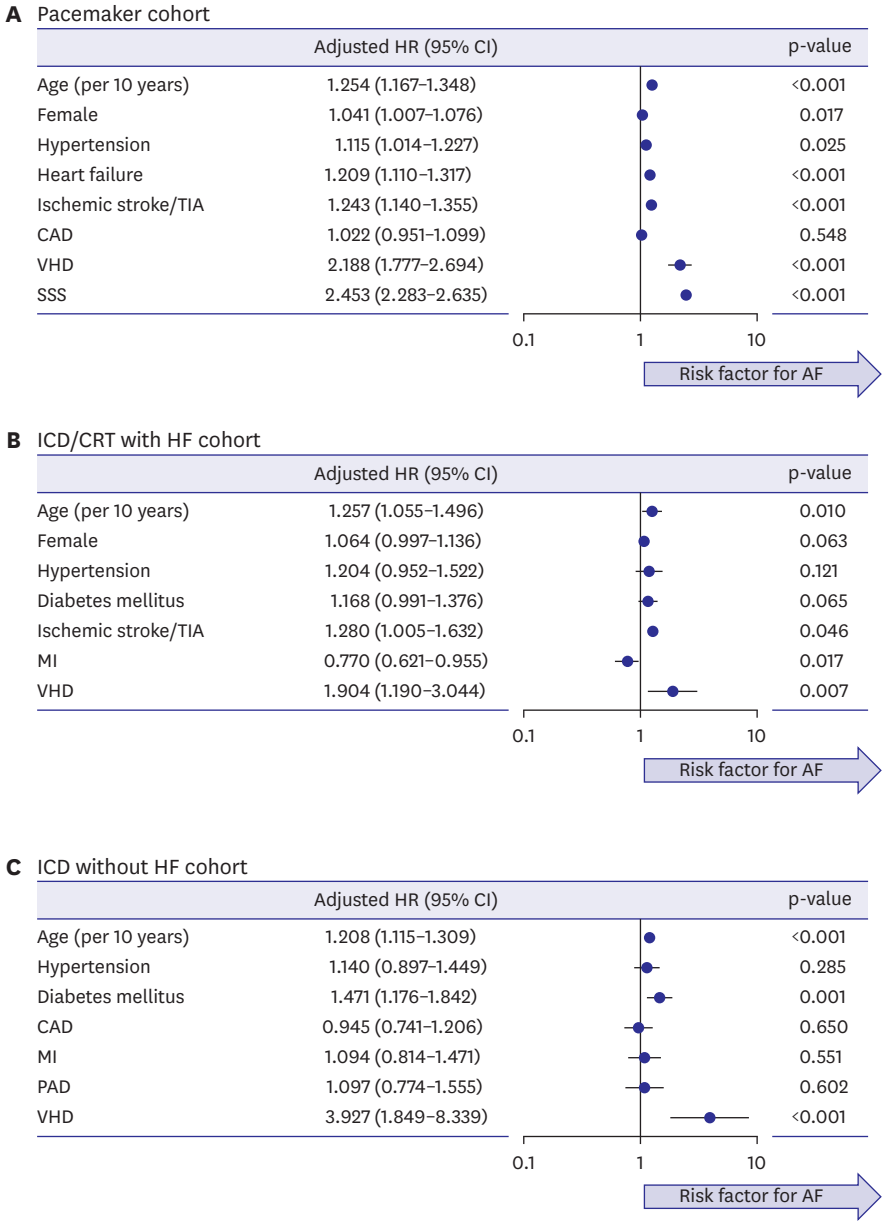

Figure 3. Factors associated with incident AF in 3 cohorts.
(A) Pacemaker cohort. (B) ICD/CRT with HF cohort. (C) ICD without HF cohort.
CAD = coronary artery disease; CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; PAD = peripheral artery disease; TIA = transient ischemic attack; SSS = sick sinus syndrome; VHD = valvular heart disease.

DISCUSSION

This comprehensive population-based cohort study included a large number of patients who had undergone CIED implantation, for which the incidence of AF with long-term follow-up was evaluated. Our major findings were as follows: 1) during follow-up, the IRs of new-onset AF were 4.3, 7.3, and 5.1 per 100 PY in patients with a pacemaker, ICD/CRT with HF, and ICD without HF; 2) older age and VHD were common risk factors associated with incident AF across the different cohorts despite additional specific risk factors in each CIED

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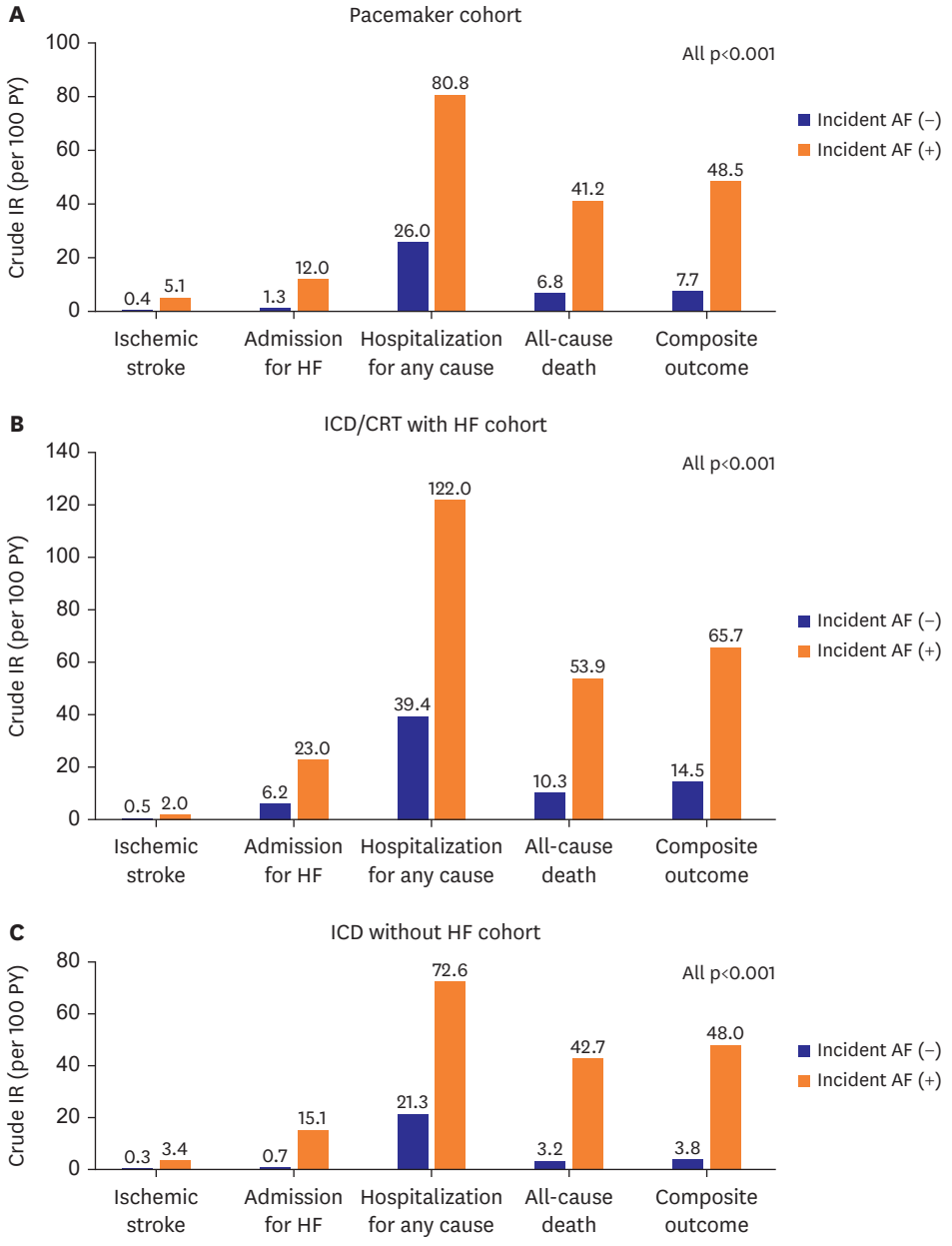

Figure 4. Crude IRs of AF-related adverse outcomes in each cohort.
AF = atrial fibrillation; CRT = cardiac resynchronization therapy; HF = heart failure; ICD = implantable cardioverter defibrillator; IR = incidence rate; PY = person-years.

cohort; 3) incident AF was associated with higher risks of ischemic stroke, admission for HF, hospitalization for any cause, all-cause death, and composite outcomes across all three cohorts; and 4) OAC prescription rates were suboptimal in CIED patients with AF, even those with a CHA_2DS_2-VASc score ≥2.

Although our study used a nationwide population-based cohort to examine the incidence, risk factors, and risk of cardiovascular adverse events of diagnosis-defined clinical AF in patients with CIED, several previous CIED cohort studies have reported the incidence of device-detected atrial arrhythmia (DDAT) based on atrial high-rate episodes (AHREs) and

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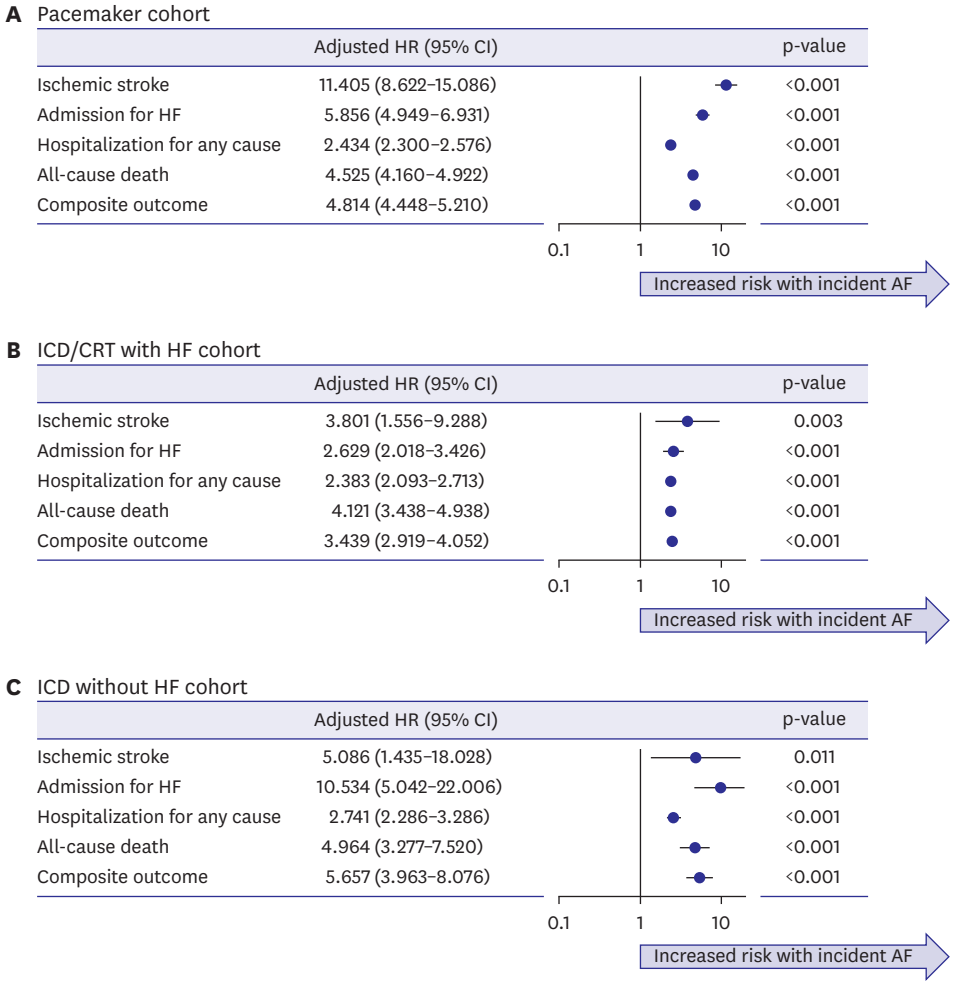

Figure 5. HRs of incident AF for AF-related adverse outcomes.
(A) Pacemaker cohort. (B) ICD/CRT with HF cohort. (C) ICD without HF cohort.
AF = atrial fibrillation; CI = confidence interval; CRT = cardiac resynchronization therapy; HF = heart failure; HR = hazard ratio; ICD = implantable cardioverter defibrillator.

analyzed its associated risk factors.[10-16] In a recent prospective multicenter study, among 816 patients with pacemakers without prevalent AF, AHREs with >6 minutes, >6 hours, and clinically documented AF by ECG were reported in 13.7%, 6.0%, and 2.9% of patients during a median follow-up of 18 months.[11] CIEDs can easily identify incident AF from subclinical to clinical AF.[10] Previous studies of CIED and AF have mainly focused on subclinical AF and its impact on the risk of thromboembolic events.[10][12][13] In a meta-analysis of 24,984 patients with CIED, including a small number of those who had undergone ICD implantation (n=321, 1.3%), 23% of patients had new-onset DDAT.[14] The risk factors for new-onset DDAT remain controversial and differ among studies. SSS and enlarged left atrium (>41 mm) were associated with a higher risk of AHREs >6 minutes, and Prior stroke/TIA, SSS and enlarged left atrium (>41 mm) were associated with a higher risk of AHREs >6 hours[11]; SSS, HF, history of recurrent TIA, and older age are reportedly related to the risk of DDAT[15][16]; or hypertension, older age, left atrial enlargement, and higher ventricular pacing burden were associated with an increased risk of the composite of DDAT and clinical AF.[17] Regarding the risk of thromboembolic events in patients with subclinical AF on CIED, although both AF burden and CHA_2DS_2-VASc scores were associated with an increased risk of thromboembolic

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events, the risk factors for stroke, defined by the CHA_2DS_2-VASc score, had a stronger association with thromboembolic risk than AF duration/burden among subclinical AF.[10)12-14)]

Although the incidence of subclinical AF in CIED patients has been highlighted,[18)] few well-organized comprehensive studies have been conducted on the development of clinical AF in CIED patients, especially in relation to the different device types and indications with sufficient numbers. This study included nationwide data on all Korean adults who had undergone CIED implantation, and evaluated the incidence of clinical AF in pacemaker, ICD/CRT with HF, and ICD without HF cohorts. Based on the device type and indication, we observed differences in baseline characteristics among them. We also observed the differences in AF incidence, the factors associated with incident AF, and the clinical significance of AF among the three cohorts depending on the differences in baseline characteristics.

Patients who had undergone pacemaker implantation were older than those in the ICD/CRT with HF cohort as well as those in the ICD without HF cohort. The baseline characteristics associated with incident AF in this study were largely consistent with those of previous studies.[14-16)] Based on our analysis, patients with SSS or mitral valve stenosis or the presence of a prosthetic heart valve might be a powerful predictor for future incident AF; thus, careful follow-up of DDAT is needed. In a recent study based on data from a claims database, AF was associated with an increased risk of ischemic stroke by 3.3-fold, HF by 3.3-fold, and all-cause death by 2.5-fold.[3)] In our study, incident AF was related to a more profound increased risk for AF-related adverse outcomes in patients with CIED. Indeed, patients with CIED might have a more severe form of "atrial myopathy" than the general population. To reduce the risk of clinical adverse events, a more holistic approach to AF management is needed, with optimal OAC therapy, rhythm control, and rate control.

Patients with ICD/CRT and HF showed the highest incidence of AF among the 3 groups. This population already had HF; thus, it could be considered as a "high-risk" population. HF is a well-known risk factor for incident AF. In patients with ICD/CRT with HF, patients with a history of myocardial infarction or presumed ischemic cardiomyopathy, had a lower risk of AF, whereas patients with VHD were associated with a higher risk of incident AF. In patients with these baseline characteristics (such as non-ischemic cardiomyopathy or VHD), the need for dual chamber ICD implantation for AF detection and differentiation might be considered and careful surveillance for DDAT at follow-up should be warranted. In addition, AF in ICD patients can cause inappropriate shock, and AF in patients with biventricular pacing can cause insufficient CRT delivery.[4)5)] Optimal OAC prescriptions and early consideration of rhythm control might be crucial for improving outcomes in the ICD/CRT with HF patients.[19)]

The last cohort we analyzed was patients who implanted ICD for secondary prevention and who did not have prevalent HF. This population has been less studied in previous research.[14)] Although the mean age was much younger than that of the pacemaker cohort, the crude IR of AF was higher. When physicians implanted ICD for secondary prevention purposes, the consideration of incident AF during long-term follow-up may not be a major concern. In our study population, the ICD without HF group had the lowest proportion of dual-chamber devices. Contrary to what physicians believe, the incidence of AF was slightly higher than that of the pacemaker cohort, which had a mean age that was almost 20 years older than the ICD without HF cohort. When we consider the detailed etiology of aborted SCD/VT/VF, both Brugada and long QT syndrome were associated with a higher risk of incident AF.[20)]

These 2 representative channelopathies are related to SSS.[21] Incident AF increased the risk of inappropriate shock in patients with Brugada syndrome, and a single-chamber device was an independent predictor of inappropriate ICD discharge.[20] Careful programming for VT/VF discrimination should be needed to avoid inappropriate shock.

The OAC prescription rate was suboptimal in CIED patients with incident AF. Although controversy persists regarding the use of OACs for subclinical AF in patients with CIED, OAC is recommended with clinical AF in the presence of stroke risk factors.[22] Considering significantly higher risk of stroke in CIED patients with incident AF, the implementation of optimal OAC treatment should be emphasized in these population.

This study has several limitations. First, this study only included East Asians from the Korean nationwide population-based database; thus, careful interpretation is needed when generalizing these results to other ethnicities and countries. Second, although the procedure and prescription claims would have been accurate because they are strictly reviewed for medical expense reimbursements, there is a possibility of under- or overestimation of the prevalence of comorbidities and outcomes. To minimize this, we adapted validated and previously used operational definitions for this study.[2][7][8] However, there is still the possibility of diagnosis input error in each diagnosis. Regarding AF, the positive predictive value of the operational definition of AF using diagnostic codes was 94.1% in a previous report from a Korean nationwide population-based cohort.[23] However, this was validated by 12-lead electrocardiogram findings in the general population. Among patients without AF in our study, a substantial proportion of these patients might have AHRE. Therefore, the data should be interpreted with caution, recognizing these limitations. Despite these limitations, our study demonstrated that patients with CIED who had clinical AF (i.e., those with a diagnosis and medical use of AF) are at increased risk for cardiovascular adverse events compared with those who do not, and highlighted the importance of defining, detecting, and managing AF in patients with CIED. Third, during the study period, the ventricular pacing strategy did not include conduction system pacing because the conduction system pacing became available in South Korea in the fourth quarter of 2019. Conventional right ventricular apical pacing could cause pacemaker-induced cardiomyopathy, and this could be one of the risk factors of incident AF.[24][25] However, in this study, we could not evaluate the occurrence of pacemaker-induced cardiomyopathy due to the limitation of not including echocardiography data.

Lastly, this database did not contain the types of AF (paroxysmal or persistent) or detailed results of device analyses; thus, the burden of AF could not be reflected in the risk of AF-related adverse outcomes.

In conclusion, a substantial proportion of patients with implanted CIED developed newly diagnosed AF. Incident AF was associated with a high risk of adverse events and the anticoagulation rate was suboptimal in patients with incident AF. Awareness, early detection, and appropriate management of AF in patients with CIED should be emphasized.

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SUPPLEMENTARY MATERIALS

Supplementary Data 1
Supplementary methods

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Supplementary Data 2
Supplementary results

Click here to view

Supplementary Table 1
Definition of cardiac implantable electronic devices, covariates, and clinical outcomes

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Supplementary Table 2
Unadjusted and adjusted hazard ratios for incident atrial fibrillation: pacemaker cohort

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Supplementary Table 3
Unadjusted and adjusted hazard ratios for incident atrial fibrillation: ICD/CRT with HF cohort

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Supplementary Table 4
Unadjusted and adjusted hazard ratios for incident atrial fibrillation: ICD without HF

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Supplementary Table 5
Baseline characteristics according to incident AF in patients with pacemaker: a 3:1 age and sex-matched cohort

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Supplementary Table 6
Baseline characteristics according to incident AF in ICD/CRT with HF: a 2:1 age and sex-matched cohort

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Supplementary Table 7
Baseline characteristics according to incident AF in ICD without HF: a 3:1 age and sex-matched cohort

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Supplementary Figure 1

Age distribution of each cohort.

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