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Association between alcohol consumption and subclinical atrial fibrillation

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Abstract

Background It has become important to identify and manage risk factors for subclinical atrial fibrillation (AF) with an increase in its detection rate. Thus, this research aimed to investigate whether alcohol consumption contributes to the development of subclinical AF.

Methods This prospective study enrolled 467 patients without AF from a multicenter pacemaker registry. The incidence of subclinical AF (episodes of atrial rate > 220 beats per minute without symptoms) was compared between alcohol-drinking and non-drinking groups.

Results During followup (median 18 months), the incidence and risk of long-duration atrial high-rate episodes (AHRE) ≥ 24 h were increased in the alcohol group compared to the non-alcohol group [5.47 vs. 2.10 per 100 person-years, adjusted hazard ratio (HR), 2.83; 95% confidence interval (CI), 1.14–7.04; $P = 0.03$]. After propensity score matching, the incidence and risk of long-duration AHRE were higher in the alcohol group (6.97 vs. 1.27 per 100 person-years, adjusted HR, 7.84; 95% CI, 1.21–50.93; $P = 0.03$). The mean burden of long-duration subclinical AF was higher in the alcohol group than in the non-alcohol group (0.18 vs. 1.61% during follow-up, $P = 0.08$).

Conclusion Alcohol consumption was associated with an increased risk of subclinical AF. Long-duration AHRE incidence and AHRE burden were higher in alcohol drinkers than in non-drinkers.

Keywords Pacemaker, Subclinical atrial fibrillation, Atrial high-rate episodes, Alcohol

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Introduction

Atrial fibrillation (AF) is associated with ischemic stroke, heart failure, hospitalization, cognitive decline, depression, and impaired quality of life, ultimately increasing mortality [1–4]. Factors known to be associated with AF include old age, hypertension, diabetes mellitus, heart failure, and valvular heart disease [5, 6].

Recognition of the detrimental relationship between alcohol and arrhythmias has been around since the 1970s [7]. The mechanism by which alcohol adversely affects ventricular conduction and alters cardiac electrophysiology is relatively clear. A dog experiment demonstrated dilation and localized swelling of the nonspecialized regions of intercalated disks in ventricular muscle and Purkinje fibers [8]. In addition, human studies have shown that alcohol causes QRS duration [9]. It is also known that QT interval and heart rate instability and variability are associated with increased risk of ventricular tachycardia and ventricular fibrillation [10].

Through major studies, the effect of alcohol on atrial electrophysiology has also been revealed. Alcohol is known to affect the atrial and pulmonary vein electrophysiology by slowing the conduction rate and reducing the effective refractory period and thus causing arrhythmia [11–13]. Alcohol consumption has been shown to be related to the occurrence and exacerbation of AF [14, 15]. Moreover, the results of a recently published study showed that the consumption of small amounts of alcohol is a risk factor for AF in addition to excessive drinking [16]. Further, abstinence from alcohol has been shown to reduce the recurrence of AF in both paroxysmal and persistent AF in patients with alcohol-induced AF [17]. Another study found that AF patients who consumed alcohol moderately or more had significantly lower AF recurrences when they ceased to drink alcohol compared to those who did not [18].

With the expanded application of cardiac implantable electronic devices (CIEDs), the detection and clinical significance of subclinical AF and atrial high-rate episodes (AHRE), including atrial tachycardia and atrial flutter, have increased. Stroke is the first symptom of AF in 25% of AF-related stroke cases, and 10% of ischemic stroke cases are caused by subclinical AF [19, 20]. Despite the clinical importance of subclinical AF/AHRE, the risk factors or predictors of AHRE have not been clearly established. In the case of alcohol, although the relationship between alcohol consumption and AF has previously been elucidated, the effect of alcohol consumption on subclinical AF remains unclear. Thus, this study aimed to assess the impact of alcohol consumption on the risk of subclinical AF.

Methods

Study population

From a prospective multicenter pacemaker registry (the AF-Pacemaker registry), we collected detailed information on device-detected subclinical AF and AHRE from 900 enrolled pacemaker patients > 18 years of age. The patients visited 11 tertiary hospital centers in Korea from September 2017 to July 2020. The details of the design of the AF-Pacemaker study are summarized in Additional file 1: Table S1. The registration and protocol of this study complied with the ethical rules of the Declaration of Helsinki (2013) of the World Medical Association and was approved by the Institutional Review Board of Yonsei University Health System (1–2017–0008). The study was also registered at Clinical-Trials.gov (NCT03303872).

The following patients were excluded from the study: (1) those younger than 18 years of age ($n=3$); (2) those with missing data from the questionnaire for alcohol consumption ($n=150$); (3) those who were already on heart rate regulation medication ($n=196$); and 4) those lost to follow-up ($n=84$). Ultimately, 467 patients were included in the study (Fig. 1). At the time of pacemaker implantation, the patients were divided into alcohol-drinking and non-drinking groups based on their alcohol consumption confirmed by asking questions from the research nurse.

Electrocardiogram assessment and followup

Patient data were collected before pacemaker implantation, including clinical information, baseline demographic characteristics, drug history, 12-lead electrocardiogram (ECG) data, 24- or 48-h Holter ECG data, treadmill test data, and transthoracic echocardiography findings. Patients with an underlying diagnosis of AF were excluded from the study, and the definition of AF was defined by ECG (12-lead ECG, 24- or 48 h Holter ECG, or treadmill test).

We confirmed whether the patients consumed alcohol through a questionnaire, and the participants were divided into alcohol and non-alcohol groups based on the results.

The electrogram analysis recorded on the devices and 12-lead ECG were performed at 6, 12, and 18 months following pacemaker implantation. Physicians were blinded to the device-recorded electrogram data during the study period. At the end of the monitoring period, the device-recorded AHRE and ECG traces were analyzed and compared based on the included data. A Clinical Events Committee identified, analyzed, and judged AHRE, deaths, and causes of death related to pacemaker implantation in a blinded manner.

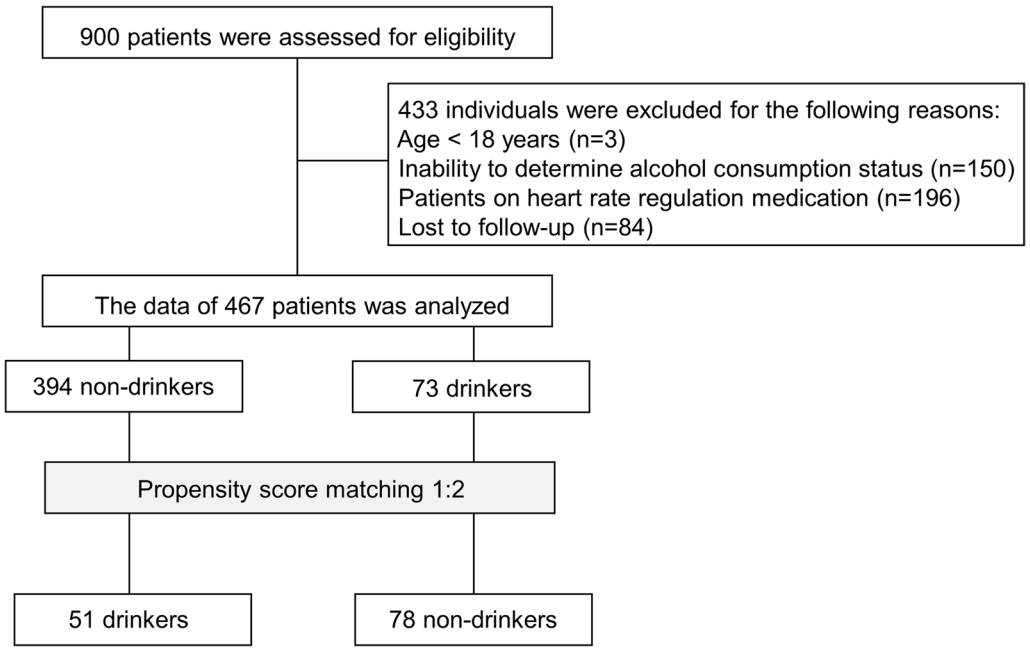

Fig. 1 Flowchart of the enrollment for analysis

Pacemaker programming and AHRE detection

All patients were implanted with the same generator (Assurity PM2272, Abbott Laboratories, Chicago, IL) and atrial and ventricular leads (Tendril MRI LPA1200M, Abbott Laboratories; Isoflex Optim 1944/1948, St Jude Medical, Saint Paul, MN; Tendril ST Optim 1888TC, Abbott Laboratories). For all procedures, the position of the leads was maintained as the right atrial appendage for the atrial lead and the right ventricular apex for the ventricular lead. AHRE is defined as events fulfilling programmed or specified criteria that are detected by an atrial lead. The device was programmed to automatically detect AHRE and record the electrocardiogram when AF or an atrial rate of 220 beats/min or higher was detected for more than 12 s [21]. At each visit, the longest duration of all the AHRE was identified and collected. The longest AHRE durations were classified as ≥ 6 min and < 6 h vs. ≥ 6 h and < 24 h vs. ≥ 24 h, respectively. The occurrence of the AHRE event was defined as the occurrence of the first event. During the observation period, all AHRE characteristics, including their incidence, duration, and burden were analyzed. Clinical events, including minor and major bleeding, cardiovascular incidents, cerebrovascular accidents, and all-cause death, were collected.

Statistical analysis

Descriptive statistics were used to analyze participant baseline characteristics. Categorical variables are presented as ratios (percentages), and continuous variables are presented as medians and interquartile ranges. Fisher's exact test or Chi-square test was performed to confirm non-random associations between categorical variables, and Student's *t*-test was performed to confirm associations between continuous variables. Propensity score matching was performed to reduce confounding biases between the alcohol and non-alcohol groups in the baseline characteristic analysis. The propensity score, which represented the probability of alcohol consumption, was estimated using a logistic regression analysis based on demographic factors and comorbidities (Table 1).

The incidence of AHRE was evaluated by dividing the number of events by person-time at risk with 95% confidence intervals (CI). Cox proportional hazard regressions were used to investigate the difference in event occurrence over time between the alcohol and non-alcohol groups, and this was expressed as a Kaplan–Meier estimate. The Cox proportional hazards assumption was checked using statistical tests based on the scaled Schoenfeld residuals.

Table 1 Baseline characteristics before and after propensity score matching

	Pre-propensity score matching				Post-propensity score matching			
	Non-alcohols ($n=394$)	Alcohols ($n=73$)	*P*	SMD	Non-alcohols ($n=78$)	Alcohols ($n=51$)	*P*	SMD
Demographics								
Age, years	73.0 (65.0–79.0)	68.0 (61.0–74.0)	< 0.01	0.46	68.5 (63.0–77.0)	69.0 (62.0–75.5)	0.70	0.08
Male sex	116 (29.5)	62 (84.9)	< 0.01	1.35	56 (71.79)	40 (78.43)	0.52	0.15
Body mass index, kg/m^2	23.9 (22.0–25.7)	24.4 (22.5–27.0)	0.09	0.18	24.2 (22.5–25.7)	23.8 (22.1–25.9)	0.82	< 0.01
Comorbidities								
Hypertension	259 (65.7)	51 (69.8)	0.58	0.09	56 (71.7)	33 (64.7)	0.51	0.15
Diabetes mellitus	112 (28.4)	16 (21.9)	0.32	0.15	21 (26.9)	12 (23.5)	0.82	0.08
Dyslipidemia	119 (30.3)	18 (24.6)	0.40	0.13	20 (25.6)	13 (25.4)	1.00	< 0.01
Previous MI	13 (3.3)	0 (0.0)	0.24	0.26	78 (100.0)	51 (100.0)	NA	< 0.01
Congestive heart failure	25 (6.3)	2 (2.7)	0.35	0.17	3 (3.8)	2 (3.9)	1.00	< 0.01
Ischemic stroke or TIA	40 (10.1)	4 (5.4)	0.30	0.17	6 (7.6)	3 (5.8)	0.97	0.07
Vascular disease	6 (1.5)	4 (5.4)	0.09	0.22	1 (1.2)	0 (0.0)	1.00	0.16
Chronic kidney disease	33 (8.3)	5 (6.8)	0.84	0.06	4 (5.1)	4 (7.8)	0.80	0.11
Echocardiographic parameters								
LA AP diameter, mm	40.0 (35.0–45.0)	41.3 (38.0–46.2)	0.07	0.06	41.0 (36.6–45.8)	41.8 (37.3–47.0)	0.53	0.09
LA volume index, mL/m^2	40.1 (31.9–53.3)	38.2 (31.9–48.4)	0.63	0.15	40.3 (33.8–50.6)	38.6 (31.5–51.0)	0.83	0.02
LVEF, %	66.0 (61.0–71.0)	63.8 (58.7–69.0)	0.11	0.18	66.0 (60.0–69.3)	63.8 (58.1–69.0)	0.44	0.10
E/E′	11.6 (8.4–15.0)	11.2 (8.9–13.7)	0.56	0.16	11.5 (9.0–14.9)	11.0 (8.3–13.9)	0.40	0.23

Values are reported as interquartile range, number (%) unless otherwise indicated

SMD Standardized mean difference; *MI* Myocardial infarction; *TIA* Transient ischemic attack; *LA* Left atrium; *AP* Anteroposterior; *LVEF* Left ventricular ejection fraction

When the two-sided *P* value was less than 0.05, it was judged to be significant. Statistical analyses were carried out with R version 4.1.2 (The R Foundation, www.R-project.org).

Results

Baseline characteristics

Compared with the alcohol group, the non-alcohol group was older (73.0 vs 68.0 years, $P<0.01$) and had fewer men (29.5% vs 84.9%, $P<0.01$). After propensity score matching, the analysis was performed with no significant difference between the two groups in the non-alcohol group vs alcohol group (71.79% vs 78.43%, $P=0.52$). Other baseline characteristics, including body mass index and comorbidities, were similar between the two groups. After propensity score matching, the baseline characteristics of the incident alcohol and non-alcohol groups were well balanced, with p values of baseline covariates < 0.05 (Table 1).

Incidence and risk of AHRE according to drinking status

During a median followup duration of 18.2 months, short (6 min and < 6 h), middle (≥ 6 h and < 24 h), and long-duration AHRE (≥ 24 h) were observed in 86 (21.8%), 28 (7.1%), and 15 (3.8%) patients out of 394 patients in the non-alcohol group, and in 16 (21.9%), seven (9.5%), and six (8.2%) patients out of 73 in the alcohol group (Table 2). The incidence of short- and middle-duration AHRE did not differ between the alcohol and non-alcohol groups. However, the incidence of long-duration AHRE was higher in the alcohol than in the non-alcohol group (5.5 vs 2.1 per 100 person-years, $P=0.03$) (Table 2). The alcohol group showed a trend of lower survival free from long-duration AHRE than the non-alcohol group (log-rank $P=0.05$, Fig. 2a). After adjustment for age, sex, and clinical variables, the alcohol group had an increased risk of long-duration AHRE with an adjusted hazard ratio (HR) of 2.83 (95% CI: 1.14–7.04, $P=0.03$) compared to the non-alcohol group (Table 2).

Table 2 Incidence and risk of AHRE according to drinking status before propensity score matching

	Patients, n	Events, n	Events /100 PYR	*P* value	Unadjusted HR (95% CI)	*P* value	Adjusted HR* (95% CI)	*P* value
AHRE (≥ 6min, < 6h)								
Non-alcohols	394	86	13.7		Reference		Reference	
Alcohols	73	16	17.2	0.40	1.16 (0.67—1.98)	0.59	1.23 (0.68—2.25)	0.50
AHRE (≥ 6h, < 24h)								
Non-alcohols	394	28	4.0		Reference		Reference	
Alcohols	73	7	6.3	0.28	1.44 (0.63—3.29)	0.38	1.20 (0.49—2.99)	0.69
AHRE (≥ 24h)								
Non-alcohols	394	15	2.1		Reference		Reference	
Alcohols	73	6	5.5	0.03	2.49 (1.00—6.36)	0.05	2.83 (1.14—7.04)	0.03

*Adjusted for age, sex, *BMI* Hypertension, *DM* Dyslipidemia, *HF* Previous, *MI* Previous peripheral disease, previous stroke/TIA

AHRE indicates atrial high-rate episode with detection rate of 220 beats/min

AHRE, atrial high-rate episode; HR, hazard ratio; CI, confidence interval; BMI, body mass index; DM, diabetes mellitus; MI, myocardial infarction; TIA, transient ischemic attack

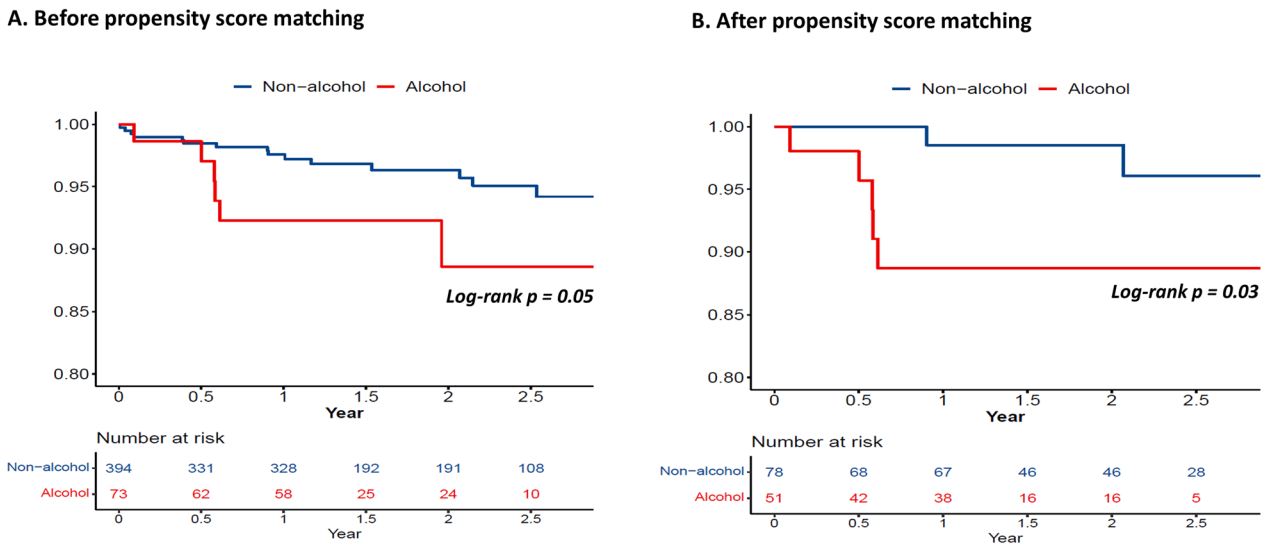

Fig. 2 Kaplan–Meier curve of free from atrial high-rate episode longer than 24 h in alcohol drinkers vs. non-drinkers. **A** Before propensity score matching. **B** After propensity score matching

After propensity score matching, the incidence of long-duration AHRE was higher in the alcohol group than in the matched non-alcohol group (7.0 vs 1.3 per 100 person-years, $P=0.03$) (Table 3). The alcohol group had a lower rate of survival free from long-duration AHRE than the matched non-alcohol group (log-rank $P=0.03$, Fig. 2b). After adjustment for age, sex, and clinical variables, the alcohol group had an increased risk of long-duration AHRE with an adjusted HR of 7.84 (95% CI: 1.21–50.9, $P=0.03$) than the matched non-alcohol group (Table 3).

Comparison of AHRE characteristics between the non-alcohol and alcohol groups

After propensity score matching, the durations of short- and middle-duration AHRE did not differ between the non-alcohol and alcohol groups. However, the duration of long-duration AHRE tended to be longer in the alcohol group than in the non-alcohol group [median 25th to 75th percentiles: 1609.45 (1494.46–1919.84) h vs. 46.36 (44.56–48.15) h, $P=0.04$] (Fig. 3, Table 4). The calculation methods for the 6-month incidence, AHRE

Table 3 Incidence and risk of AHRE according to drinking status after propensity score matching

	Patients, n	Events, n	Events /100 PYR	*P* value	Unadjusted HR (95% CI)	*P* value	Adjusted HR* (95% CI)	*P* value
AHRE (≥ 6min, < 6h)								
Non-alcohols	78	14	9.63		Reference		Reference	
Alcohols	51	11	18.22	0.10	1.68 (0.77—3.65)	0.19	1.57 (0.68—3.62)	0.29
AHRE (≥ 6h, < 24h)								
Non-alcohols	78	7	4.53		Reference		Reference	
Alcohols	51	7	9.75	0.14	2.02 (0.72—5.67)	0.18	1.56 (0.53—4.58)	0.42
AHRE (≥ 24h)								
Non-alcohols	78	2	1.27		Reference		Reference	
Alcohols	51	5	6.97	0.02	4.91 (1.09—22.15)	0.03	7.84 (1.21—50.93)	0.03

*Adjusted for age, sex, BMI, hypertension, DM, dyslipidemia, HF, previous MI, previous peripheral disease, previous stroke/TIA

AHRE indicates atrial high-rate episode with detection rate of 220 beats/min

AHRE Atrial high-rate episode; *HR* Hazard ratio; *CI* Confidence interval; *BMI* Body mass index; *DM* Diabetes mellitus; *MI* Myocardial infarction; *TIA* Transient ischemic attack

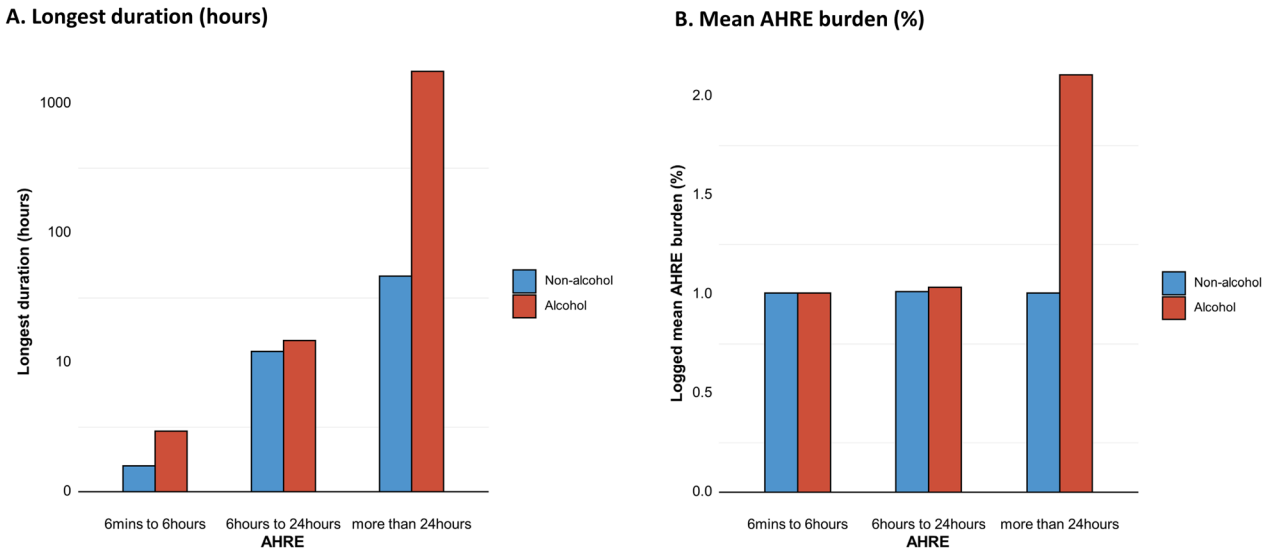

Fig. 3 Burden of atrial high-rate episodes in alcohol drinkers vs. non-drinkers after propensity score matching. **A** Longest duration (h) **B** Logged Mean AHRE burden (%) AHRE, atrial high-rate episodes

duration, and AHRE burden are shown in Additional file 1: Figs. S1, S2, and S3, respectively.

Discussion

In this study, among patients who underwent pacemaker implantation with sick sinus syndrome or atrioventricular node disease without a history of AF, the occurrence of long-duration AHRE was significantly higher in the patients who consumed alcohol than in those who did not. Moreover, long-duration AHRE, but not short- or middle-duration AHRE, was more burdensome for patients who consumed alcohol than for those who did not. These findings suggest that alcohol consumption is associated with long-duration subclinical AF and supports the abstinence of alcohol for improved cardiac outcomes.

Clinical implications of long-duration AHRE

The incidence of subclinical AF and AHRE in patients using CIED such as pacemakers is reported as 30–70% [22, 23]. Previous studies have shown that short episodes of 10–20 s/day are clinically significant. This is because these short episodes are not associated with clinically meaningful long episodes and are not risk factors for systemic embolisms such as stroke, myocardial infarction, or pulmonary thromboembolism [24]. However, subclinical

Table 4 Comparison of AHRE characteristics after propensity score matching

	Non-alcohol group ($n=78$)	Alcohol group ($n=51$)	*P* value
AHRE (≥ 6 min, < 6 h)			
6-Month Incidence	0.09	0.27	< 0.01
Duration (h/person)			
Sum (h)	38.73 ± 60.95	67.20 ± 57.55	0.25
Mean (h)	9.50 ± 10.88	12.88 ± 8.53	0.41
Longest (h)	15.86 ± 18.83	29.56 ± 17.24	0.07
Mean AHRE Burden (%)	0.01 ± 0.03	0.01 ± 0.03	0.42
AHRE (≥ 6 h, < 24 h)			
6-Month incidence	0.03	0.09	0.08
Duration (h/person)			
Sum (h)	161.69 ± 84.33	251.98 ± 180.60	0.25
Mean (h)	112.30 ± 50.87	130.14 ± 43.91	0.50
Longest (h)	121.90 ± 55.87	148.12 ± 50.29	0.37
Mean AHRE burden (%)	0.02 ± 0.10	0.05 ± 0.20	0.34
AHRE (≥ 24)			
6-Month incidence	0.01	0.09	0.34
Duration (h/person)			
Sum (h)	463.56 ± 25.33	24,258.03 ± 15,571.03	0.03
Mean (h)	463.56 ± 25.33	14,057.83 ± 14,542.15	0.11
Longest (h)	463.56 ± 25.33	17,747.07 ± 13,201.33	0.04
Mean AHRE burden (%)	0.01 ± 0.06	2.31 ± 8.28	0.05

AHRE burden (%); Duration of AHRE ((< 6 min, 6 min to 24 h, and ≥ 24 h, respectively) per person for the total followup period

AHRE Atrial high-rate episode with detection rate of 220 beats/min. *AHRE* Atrial high-rate episode

AF and AHRE longer than 5–6 min are related to a risk of developing clinical AF [19, 25], ischemic stroke [19, 20], all-cause mortality [26], and cardiovascular events [27, 28].

There is a time difference between the onset of subclinical AF and AHRE and the onset of acute stroke; therefore, it is reasonable to view them as markers rather than direct risk factors for stroke [2, 29]. Furthermore, although the correlation between AHRE and embolic stroke of unknown etiology remains unclear, the results of previous studies suggest that the duration of AHRE is clearly associated with the incidence of systemic thromboembolism, including ischemic stroke [30, 31].

Long-duration AHRE have been found to be clinically significant, and the European Society of Cardiology guidelines suggest consideration of oral anticoagulant (OAC) use in long-duration subclinical AF and AHRE (≥ 24 h) when the patient's risk of stroke is high [2]. However, although the association between AHRE/subclinical AF and stroke has previously been demonstrated and several studies are in progress [32], optimal primary treatment for stroke prevention remains uncertain and there are no specific guidelines for the use of OAC in these patients as evidence for the use of OAC for AHRE remains insufficient. Therefore, it is necessary to identify and manage the stroke risk factors in these patients.

One previous study proposed stratification of management strategies for patients with AHRE based on episode duration [33]. In that study, AHRE were divided into three groups: duration < 6 min to 24 h, duration ≥ 24 h, and duration of 24 h. Patients with an AHRE duration of 24 h were encouraged to consider anticoagulation therapy according to the guidelines for AF patients. In our study, we divided the patients into three groups based on the same criteria and analyzed the effect of alcohol consumption on the occurrence of AHRE.

Alcohol and subclinical AF

It is known that subclinical AF is related to systemic embolism, and in one large stroke registry, approximately 9% of ischemic stroke cases were found to be related to subclinical AF [30]. A study reported that 161 of 476 subclinical AF patients had an increased risk of mortality from all causes, not solely cardiovascular death, compared to AF with typical symptoms. The result was the same after adjusting for related variables [34]. In another study, subclinical AF was found in 1.4% of the general population aged above 65 years in a screening test, with AF persistent at followup [35, 36]. As such, the clinical significance of subclinical AF is well-established.

Despite the clinical importance of subclinical AF/AHRE, the risk factors or predictors of AHRE have not been clearly established. The same is true for alcohol use as an AF risk factor. In this context, the approach to risk factors and predictors of AHRE should be made separately. Alcohol consumption has already been shown to be related to the occurrence and exacerbation of AF; however, the association between alcohol consumption and subclinical AF has not been well identified.

In our study, AHRE for less than 24 h did not differ significantly among the alcohol and non-alcohol groups, whereas AHRE for more than 24 h did show a significant difference in outcomes between the two groups. Furthermore, when divided into three groups (duration < 6 min to 24 h, duration ≥ 24 h, and duration of 24 h), there was a trend of an increase in the number of events and cumulative burden as the duration increased. This suggests that alcohol consumption is an independent risk factor for long-duration AHRE. This study will be an important step in the study of the relationship between alcohol and AHRE and further evaluation on risk factor for assessment and management of AHRE.

Study limitations

This study had some limitations. First, as a prospective and multicenter study, a basis for the results was secured; however, it had limitations as a non-randomized and observational study. Second, while this study evaluated the relationship between alcohol consumption and the incidence of AHRE, we were unable to assess the type or quantity of alcohol consumed and further research is needed. An analysis of consumption by period is also needed. Third, as the study period was relatively short and there were fewer enrolled patients in comparison with that in previous studies, changes in drinking status over time could not be tracked. Fourth, the number of patients included in the analysis was small and larger randomized studies are needed. Fifth, this study includes sub-analyses that examine AHRE based on their duration, which may introduce selection bias if events of certain durations are excluded from certain groups. Finally, due to the short observation period, clinical events could not be analyzed. Long-term data are required to validate the results.

Conclusions

Alcohol consumption is a critical risk factor for subclinical AF. In particular, long-duration AHRE and the burden of AHRE are higher in alcohol drinkers than in non-drinkers.

Abbreviations

AF	Atrial fibrillation
AHRE	Atrial high-rate episodes
CI	Confidence intervals
CIED	Cardiac implantable electronic device
ECG	Electrocardiogram
HR	Hazard ratio
OAC	Oral anticoagulant

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s42444-023-00102-5.

Additional file 1: **Table S1**. Summary of the AF-pacemaker study design. **Figure S1**. Calculation of the 6-month incidence. **Figure S2**. Calculation of AHRE duration. **Figure S3**. Calculation of AHRE duration.

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None.

Author contributions

Conceptualization GY and DK; Methodology HY and TK; Software JS; Validation IO, JP and HP; Formal analysis GY; Investigation YL; Resources KK; Data curation DK; Writing—original draft preparation GY; Writing—review and editing DK; Visualization JS; Supervision EC; Project administration BJ; Funding acquisition BJ. All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials

The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate

The present study's enrollment and protocol followed the ethical rules of the Declaration of Helsinki (2013) of the World Medical Association and was approved by the Institutional Review Board of Yonsei University Health System (1–2017–0008). The study was also registered at ClinicalTrials.gov (NCT03303872).

Informed consent

Informed consent was obtained from all subjects involved in the study.

Competing interests

The authors declare that they have no conflict of interest.

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