Effect of alcohol consumption on the risk of adverse events in atrial fibrillation: from the COmparison study of Drugs for symptom control and complication prEvention of Atrial Fibrillation (CODE-AF) registry

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Aims	The aim of this study is to determine the relationship between alcohol consumption and atrial fibrillation (AF)-related adverse events in the AF population.
Methods and results	A total of 9411 patients with nonvalvular AF in a prospective observational registry were categorized into four groups according to the amount of alcohol consumption—abstainer-rare, light (<100 g/week), moderate (100–200 g/week), and heavy (≥200 g/week). Data on adverse events (ischaemic stroke, transient ischaemic attack, systemic embolic event, or AF hospitalization including for AF rate or rhythm control and heart failure management) were collected for 17.4 ± 7.3 months. A Cox proportional hazard models was performed to calculate hazard ratios (HRs), and propensity score matching was conducted to validate the results. The heavy alcohol consumption group showed an increased risk of composite adverse outcomes [adjusted hazard ratio (aHR) 1.32, 95% confidence interval (CI) 1.06–1.66] compared with the reference group (abstainer-rare group). However, no significant increased risk for adverse outcomes was observed in the light (aHR 0.88, 95% CI 0.68–1.13) and moderate (aHR 0.91, 95% CI 0.63–1.33) groups. In subgroup analyses, adverse effect of heavy alcohol consumption was significant, especially among patients with low CHA_2DS_2-VASc score, without hypertension, and in whom β-blocker were not prescribed.
Conclusion	Our findings suggest that heavy alcohol consumption increases the risk of adverse events in patients with AF, whereas light or moderate alcohol consumption does not.
Keywords	Alcohol consumption • Heavy drinking • Atrial fibrillation • Stroke • Hospitalization • Registry

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> ## What's new?
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> - Heavy alcohol consumption (≥200 g/week) increases the risk of atrial fibrillation (AF)-related adverse events (thromboembolic events and AF-related hospitalization) in patients with AF significantly.
> - Whereas there was no significant increased or decreased risk with light or moderate alcohol consumption.
> - The association between heavy drinking and AF-adverse events is highly significant, particularly in the AF population with fewer morbidities who are therefore considered less vulnerable.

Introduction

Humans have a long history of alcohol consumption. For a long time, drinking alcohol has been shown to be linked to many human diseases, and its attributable burden on global diseases was estimated to be 5.5% in 2010 World Health Organization report.[1] Many studies have been conducted to reveal the relationship between alcohol consumption and cardiovascular (CV) events in the general population, and it has been demonstrated that drinking alcohol could positively or negatively affect CV events in various ways.[2–6] In particular, alcohol consumption is significantly associated with an increased risk for atrial fibrillation (AF).[3,7]

However, the dose-dependent effects of alcohol on CV events is still inconclusive, as many previous studies have not only demonstrated the cardioprotective effects of light-to-moderate alcohol drinking[4,6] but also the cardiotoxic effects of heavy alcohol drinking, known as the 'alcohol paradox'.[7] Furthermore, little is known about the association between alcohol consumption and CV events in patients with AF. Although current AF management guidelines have described that heavy alcohol consumption is associated with an increased incidence of AF in the general population and increased bleeding risk in the AF population,[8] there are no specific recommendations or warnings for controlling alcohol consumption in patients with prevalent AF.

This study aimed to (i) determine the association between alcohol consumption and possible AF-related adverse events, including thromboembolic events, AF-related hospitalization, death, and major bleeding; and (ii) assess the dose–response relationship between the amount of alcohol consumption and AF-related adverse events in the AF population.

Methods

Study population

The COmparison study of Drugs for symptom control and complication prEvention of Atrial Fibrillation (CODE-AF) registry is an ongoing prospective observational registry at 18 tertiary hospitals from all geographical regions of South Korea. Detailed descriptions are available in previous studies.[9] In brief, the aim of this registry is to assess the clinical epidemiology of patients with AF, as well as to determine the diagnostic and therapeutic processes applied in these patients, and the clinical outcomes. All patients provided informed consent. The registry was designed by the

Korea Heart Rhythm Society, approved by the ethics committee of each centre (4-2016-0105), and registered at ClinicalTrials.gov (NCT02786095).

A total of 10 855 subjects with primary diagnosis of nonvalvular AF and aged older than 18 years were enrolled from June 2016 to May 2019. Pregnant or breast-feeding women, participants whose expected survival time was <1 year, participants with transient AF caused by reversible conditions (e.g. hyperthyroidism, pulmonary embolism, and post-operative condition), and participants requiring chronic anticoagulation (e.g. pulmonary embolism and deep vein thrombosis) were excluded from our study. After enrolment, a total of 1444 subjects without available alcohol consumption data ($n = 228$), without available clinical event data due to a short follow-up period (<6 months before the first clinic visit) ($n = 1163$), as well as those who met the exclusion criteria due to valvular AF ($n = 34$), required chronic anticoagulation for other diseases ($n = 10$), and had transient AF caused by reversible conditions ($n = 9$) were excluded from the final analysis (Figure 1).
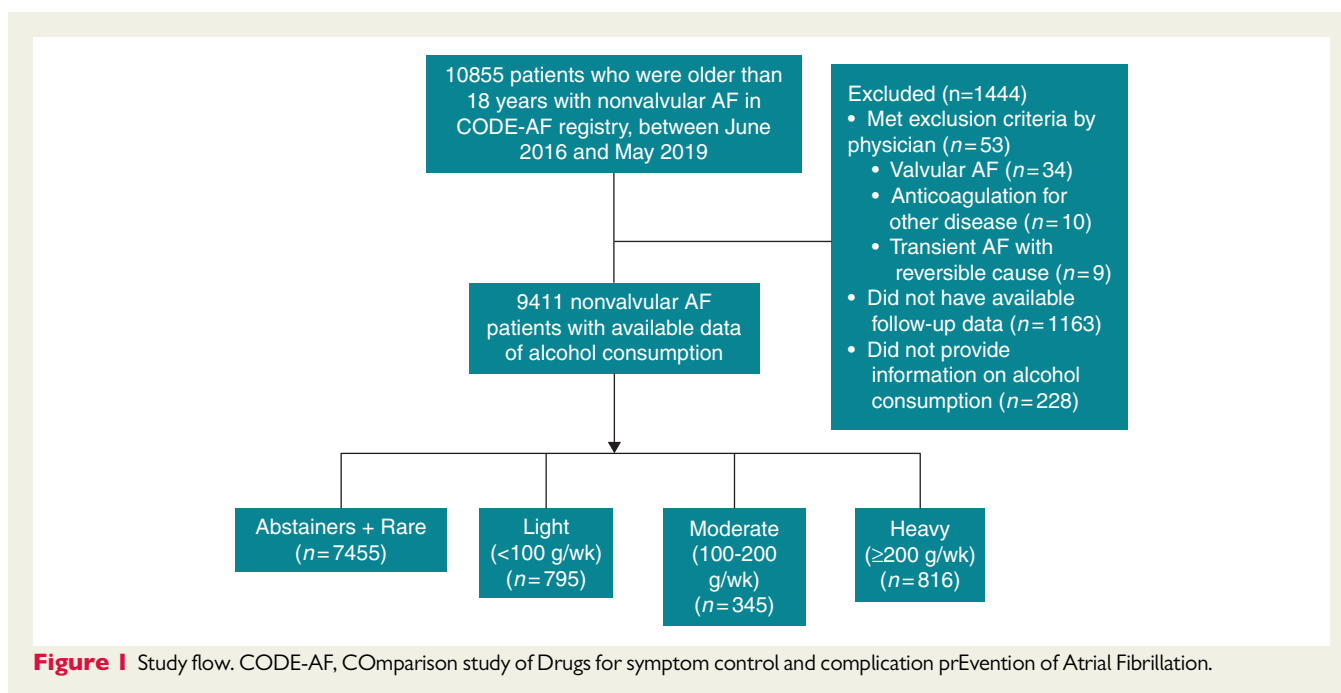
Alcohol consumption

All subjects were required to provide information regarding their alcohol drinking habits in the past 3 years from enrolment. The amount of alcohol consumed at each time and the drinking frequency per week were multiplied to obtain the amount of alcohol consumption per week. After reviewing previous studies and the National Institute on Alcohol Abuse and Alcoholism (NIAAA)'s definition of moderate drinking (>14 drinks for men and >7 drinks for women),[4,7,10,11] we categorized the subjects into alcohol consumption groups according to the grams of ethanol consumed per week. Abstainers were defined as those who did not drink any alcoholic beverage in past 3 years, and rare drinkers were defined as those who drink alcohol occasionally (less than once a month), usually in a social setting. Light (>0–100 g), moderate (100–200 g), and heavy (≥200 g) drinkers were defined according to the weekly alcohol consumption amount. Abstainers plus rare drinkers were used as a reference group for analysing the risk compared with other groups in our study.

Covariates and adverse events of atrial fibrillation

Among the collected covariates in our registry, age, sex, history of hypertension, diabetes, congestive heart failure, previous ischaemic stroke, transient ischaemic attack (TIA), vascular disease, including myocardial infarction and peripheral artery disease, dyslipidaemia, chronic kidney disease, cancer, and smoking status were used as clinical factors to adjust the risk for adverse events.

Atrial fibrillation-related adverse events included thromboembolic events [ischaemic stroke, TIA, systemic embolic event (SEE)], AF hospitalization (hospitalization for rate or rhythm control of AF and heart failure management), death (of any cause), and major bleeding (fatal bleeding or overbleeding with a decrease in haemoglobin level of >2 g/day or requiring transfusion of >2 units of packed red blood cells). These events were collected every 6 months during regular clinic visits.

The primary outcome was defined as a composite of thromboembolic events and AF-related hospitalization to focus on the prognosis of AF. Thromboembolic events are the most serious complication of AF and the prevention of these events is the major target of medical therapy. Atrial fibrillation hospitalization has been used as a surrogate marker of death and combined endpoints in several previous AF population studies. Since this study population consisted of patients who had AF as a primary diagnosis, HF hospitalization was included in AF-related hospitalization. Detailed cause of hospitalization is presented in Supplementary material online, Table S2. Death was chosen as a secondary outcome and not included in primary endpoint, as the subjects were enrolled at early stage of

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┌─────────────────────────────┐       ┌─────────────────────────────┐
│ 10855 patients who were     │       │ Excluded (n=1444)           │
│ older than 18 years with    │       │ • Met exclusion criteria by │
│ nonvalvular AF in CODE-AF    │       │   physician (n=53)          │
│ registry, between June      │       │   • Valvular AF (n=34)      │
│ 2016 and May 2019           │       │   • Anticoagulation for     │
└─────────────────────────────┘       │     other disease (n=10)    │
                                       │   • Transient AF with       │
                                       │     reversible cause (n=9)  │
                                       │ • Did not have available    │
          ┌─────────────────────────┐ │   follow-up data (n=1163)   │
          │ 9411 nonvalvular AF     │ │ • Did not provide           │
          │ patients with available │ │   information on alcohol    │
          │ data of alcohol         │ │   consumption (n=228)       │
          │ consumption             │ └─────────────────────────────┘
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Abstainers + Rare (n=7455)   Light (<100 g/wk) (n=795)   Moderate (100–200 g/wk) (n=345)   Heavy (≥200 g/wk) (n=816)

Figure 1 Study flow. CODE-AF, COmparison study of Drugs for symptom control and complication prEvention of Atrial Fibrillation.

AF and follow-up duration was not long enough (mean 17.4 ± 7.3 months) to detect the long term adverse effect of alcohol. Major bleeding event, which is not a CV event, was also chosen as a secondary outcome, as it is a major outcome especially among anticoagulated AF patients. The secondary outcomes included components of adverse events (thromboembolic events, AF-related hospitalization, death, or major bleeding) and extended composite adverse events (primary outcome or death and primary outcome, death, or major bleeding).

Statistical analysis

Continuous variables are expressed as mean ± standard deviation and compared using analysis of variance. Categorical variables are reported as frequencies (percentage) and compared using the χ^2 or Fisher's exact tests. The incident rates of adverse events were calculated as the number of events per 100 person-years with confidence intervals (CIs) in four groups.

Hazard ratios (HRs) are presented as unadjusted, age- and sex-adjusted, and clinical factor-adjusted, using Cox proportional hazard models with adjustment for clinical factors, which is significantly associated with primary endpoint (thromboembolic events, CV events, and HF hospitalization); age, sex, history of hypertension, diabetes, congestive heart failure, previous ischaemic stroke, TIA, vascular disease, dyslipidaemia, chronic kidney disease, smoking status, and cancer status. Propensity score (PS) matching analysis was performed to validate the results in multivariate Cox regression analysis. Propensity score was used to correct for potential systematic differences between abstainer-rare and each drinker groups in a 2 : 1 manner using a logistic regression model. Propensity score matching was made on logit-transformed PS matched to the nearest neighbour with a caliper of 0.1. No replacements were used. Clinical variables for multivariate Cox regression analysis and anticoagulant prescription were used for PS matching. All variables used for matching were well-balanced (standardized differences <0.1) (Supplementary material online, Figure S1). Continuous HRs are presented to show the dosing effects of alcohol consumption using cubit spline curves. All analyses were performed using SPSS 25.0 for Windows

(SPSS Inc., Chicago, IL, USA) and R statistical software, version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria). A *P*-value <0.05 was considered statistically significant.

Results

A total of 9411 subjects were eligible and categorized into four groups according to alcohol consumption amount: abstainer-rare (0 g/week), light (<100 g/week), moderate (100–200 g/week), and heavy (≥200 g/week) groups. The number of patients in each group was 7455 (79.2%), 795 (8.4%), 345 (3.7%), and 816 (8.7%), respectively.

Table 1 shows the baseline characteristics of the study population according to alcohol consumption. Subjects with more alcohol consumption were more likely to be male, younger, and with a lower CHA_2DS_2-VASc score. A total of 975 (10.4%) adverse events including ischaemic stroke, TIA, SEE, AF hospitalization, death, or major bleeding occurred during the follow-up period (mean 17.4 ± 7.3 months). Detailed data of each adverse event according to alcohol consumption are reported in Supplementary material online, Table S1.

The incident rate of adverse events according to alcohol consumption is shown in *Table 2*. *Figure 2* shows a J-shaped relationship between the alcohol consumption amount and the risk of primary composite outcome in the AF population. Until an alcohol consumption of 135 g/week, the risk was HR <1.0; however, after 135 g/week, the risk was higher than that of the reference group.

Adjusted HRs (aHRs) for primary composite outcome according to alcohol consumption are presented in *Table 3*. Patients in the heavy group had an increased risk for the primary composite outcome compared with those in the reference group (aHR 1.32, 95% CI 1.06–1.66). Conversely, the light (aHR 0.88, 95% CI 0.68–1.13)

Table 1 Baseline characteristics of subjects according to alcohol consumption

	Alcohol consumption				
	Abstainers and rare[a] (n = 7455)	Light (<100 g/week) (n = 795)	Moderate[b] (100–200 g/week) (n = 345)	Heavy (≥200 g/week) (n = 816)	P-Value
Age (years)	68.3 ± 10.6	63.9 ± 11.1	61 ± 10.6	60.4 ± 10.6	<0.01
<65	2502 (33.6)	400 (50.3)	213 (61.7)	538 (65.9)	
65–74	2621 (35.2)	251 (31.6)	93 (27.0)	200 (24.5)	
≥75	2332 (31.3)	144 (18.1)	39 (11.3)	78 (9.6)	
Female sex	3268 (43.8)	82 (10.3)	16 (4.6)	18 (2.2)	<0.01
CHA2DS2-VASc score[c]	2.9 ± 1.7	2.0 ± 1.5	1.7 ± 1.4	1.7 ± 1.3	0.00
Hypertension	4991 (66.9)	490 (61.6)	222 (64.3)	529 (64.8)	0.02
Diabetes	1899 (25.5)	172 (21.6)	68 (19.7)	202 (24.8)	0.01
Heart failure	757 (10.2)	52 (6.5)	27 (7.8)	94 (11.5)	<0.01
Vascular disease	513 (6.9)	49 (6.2)	17 (4.9)	38 (4.7)	0.05
MI	223 (3.0)	21 (2.6)	6 (1.7)	16 (2.0)	0.20
PAD	437 (5.9)	43 (5.4)	15 (4.3)	31 (3.8)	0.07
Ischaemic stroke or TIA	1199 (16.1)	89 (11.2)	39 (11.3)	76 (9.3)	<0.01
CKD	820 (11.0)	53 (6.7)	14 (4.1)	32 (3.9)	<0.01
Dyslipidaemia	2651 (35.6)	270 (34)	100 (29)	249 (30.5)	<0.01
Cancer	801 (10.7)	60 (7.5)	26 (7.5)	47 (5.8)	<0.01
Smoking status					<0.01
Current	337 (5.1)	106 (13.3)	86 (24.9)	252 (30.9)	
Former	1561 (20.9)	283 (35.6)	124 (35.9)	299 (36.6)	
BMI (kg/m^2)	24.5 ± 3.4	24.8 ± 2.9	25.2 ± 3.2	25.4 ± 3.2	<0.01
≥30	432 (5.8)	37 (4.7)	25 (7.2)	68 (8.3)	0.01
SBP (mmHg)	122.3 ± 15.7	123.0 ± 14.3	124.3 ± 14.1	125.2 ± 14.5	<0.01
DBP (mmHg)	74.3 ± 11.7	76.9 ± 11.1	79.0 ± 12.1	78.9 ± 12.0	<0.01
Heart rate (beats/min)	76.3 ± 17.2	75.1 ± 15.5	76.1 ± 16.2	78.2 ± 16.5	<0.01
AST (IU/L)	25.4 ± 13.5	25.6 ± 12.8	26.6 ± 10.1	29.8 ± 17.6	<0.01
ALT (IU/L)	23.1 ± 18.3	24.5 ± 23.3	24.8 ± 11.5	27.1 ± 17.4	<0.01
Total bilirubin (mg/dL)	0.81 ± 0.47	0.90 ± 0.41	0.88 ± 0.39	0.89 ± 0.38	<0.01
LVEF (%)	61.0 ± 14.1	60.7 ± 8.3	60.4 ± 9.4	59.2 ± 1.0	0.01
Type of AF at enrolment					0.05
Paroxysmal	4898 (65.7)	501 (63.0)	212 (61.4)	488 (59.8)	
Persistent	2329 (31.2)	267 (33.6)	122 (35.4)	296 (36.3)	
Permanent	228 (3.1)	27 (3.4)	11 (3.2)	32 (3.9)	
Medication					
Anticoagulation	5448 (73.1)	508 (63.9)	204 (59.1)	527 (64.6)	<0.01
NOAC	4317 (57.9)	354 (44.5)	157 (45.5)	423 (51.8)	<0.01
Antiarrhythmic agent	3505 (47.0)	437 (55.0)	181 (52.5)	419 (51.3)	<0.01
Antiplatelet agent	1760 (23.6)	220 (27.7)	105 (30.4)	221 (27.1)	<0.01
Statin	2573 (34.5)	235 (29.6)	102 (29.6)	243 (29.8)	<0.01
β-Blocker	3596 (48.3)	362 (45.5)	176 (51.0)	419 (51.4)	0.09
RAS blockade	2937 (39.4)	266 (33.5)	126 (36.5)	356 (43.6)	<0.01
CCB	2071 (27.8)	197 (24.8)	89 (25.8)	237 (29.1)	0.19

AF, atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; CCB, calcium channel blocker; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NOAC, new oral anticoagulant; PAD, peripheral artery disease; RAS, renin–angiotensin system.
[a]Defined as alcohol consumption of no more than once per week or a few times each month.
[b]Considering the National Institute on Alcohol Abuse and Alcoholism definition and previous studies, moderate alcohol consumption was defined as 100–200 g/week.
[c]The CHA2DS2-VASc score is a stroke risk scoring system, from 0 to 9, in which higher point indicates a higher risk for stroke.

Table 2 Incident rate of adverse events according to alcohol consumption

Number of events/100 person-year (95% CI)	Alcohol consumption			
	Abstainers and rare	Light (<100 g/week)	Moderate (100–200 g/week)	Heavy (≥200 g/week)
Primary composite outcome[a]	6.73 (6.23–7.25)	5.77 (4.47–7.32)	6.44 (4.34–9.19)	9.65 (7.87–11.71)
Secondary composite outcome 1[b]	7.33 (6.81–7.88)	6.11 (4.77–7.71)	6.65 (4.52–9.44)	9.65 (7.87–11.71)
Secondary composite outcome 2[c]	7.65 (7.12–8.21)	6.54 (5.15–8.19)	6.87 (4.70–9.69)	9.84 (8.04–11.92)
Ischaemic stroke and TIA and SEE	0.98 (0.80–1.20)	0.60 (0.24–1.24)	0.64 (0.13–1.88)	1.13 (0.59–1.98)
AF hospitalization[d]	5.85 (5.39–6.35)	5.34 (4.09–6.84)	5.79 (3.82–8.43)	8.61 (6.93–10.57)
Death	0.75 (0.59–0.94)	0.43 (0.14–1.00)	0.21 (0.05–1.20)	0.28 (0.06–0.83)
Major bleeding	0.54 (0.41–0.71)	0.60 (0.24–1.24)	0.86 (0.23–2.20)	0.47 (0.15–1.10)

AF, atrial fibrillation; CI, confidence interval; SEE, systemic embolic event; TIA, transient ischaemic attack.
[a]Primary composite outcome including ischaemic stroke, TIA, SEE, and AF hospitalization.
[b]Secondary composite outcome 1 including ischaemic stroke, TIA, SEE, AF hospitalization, and death.
[c]Secondary composite outcome 2 including ischaemic stroke, TIA, SEE, AF hospitalization, death, and major bleeding.
[d]AF hospitalization was defined as hospitalization for AF rate or rhythm control and heart failure management.
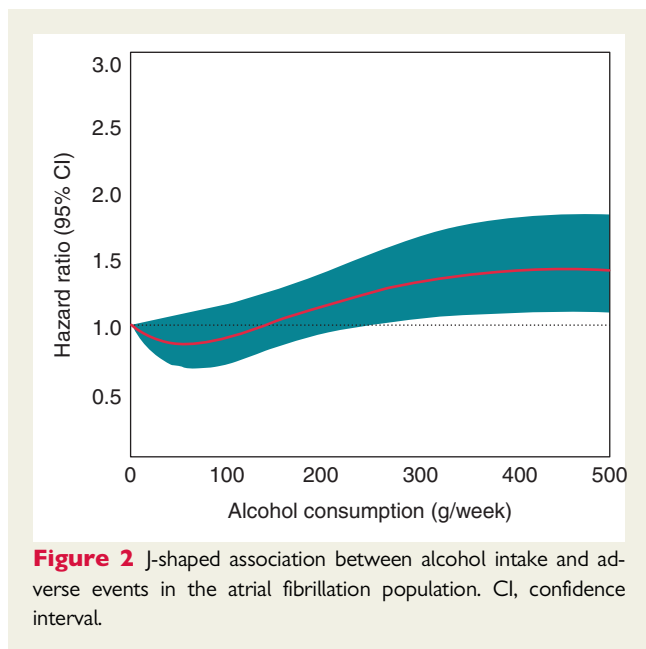

Figure 2 J-shaped association between alcohol intake and adverse events in the atrial fibrillation population. CI, confidence interval.

and moderate (aHR 0.91, 95% CI 0.63–1.33) groups did not show a significant difference in the risk for the primary composite outcome compared with the reference group (Table 3). The HRs for death, major bleeding, hospitalization, and two extended secondary composite outcomes (primary outcome or death and primary outcome, death, or major bleeding) are presented in Supplementary material online, Table S3. Increased risk of primary composite outcomes was mainly driven by increased risk of AF hospitalization (aHR 1.28, 95% CI 1.01–1.63). However, risk of death and risk of major bleeding were not significantly different across all groups.

After PS matching between the abstainer-rare and heavy groups to adjust variables, including stroke risk factors and oral anticoagulant prescription, additional analyses for the risk of all adverse events were performed, and the results are shown in Table 4. In the heavy group, the primary composite outcome (aHR 1.48, 95% CI 1.14–1.92), secondary composite outcome including primary composite outcome and death and major bleeding (aHR 1.42, 95% CI 1.10–1.83), ischaemic stroke/TIA or SEE (aHR 2.27, 95% CI 0.99–5.19), and AF hospitalization (aHR 1.39, 95% CI 1.06–1.82) showed significantly increased risks compared with those in the abstainer-rare group. After PS matching, the light and moderate groups still did not show any significant difference in the risk for all adverse events compared with the reference group (Supplementary material online, Tables S4 and S5).

In subgroup analysis, heavy alcohol consumption was associated with an increased adverse events among the AF population with a low risk of stroke (CHA_2DS_2-VASc score 0 in men and 1 in women) (aHR 2.45, 95% CI 1.57–3.84), and those without hypertension (aHR 1.61, 95% CI 1.14–2.28), without a history of use of β-blockers (aHR 1.67, 95% CI 1.21–2.29) or antiplatelet agents (aHR 1.44, 95% CI 1.13–1.85), and with mean heart rate ≥100/min in baseline Holter monitoring (aHR 1.59, 95% CI 1.17–2.16) (Figure 3).

Discussion

There were ~8000 light-to-heavy drinkers and 2000 abstainers and rare drinkers with AF in this study. Heavy alcohol consumption was significantly associated with increased risks of composite adverse events of AF, including ischaemic stroke, TIA, SEE, or AF hospitalization. However, no significant relationship was observed between light or moderate alcohol consumption and the risk for primary composite outcomes. A J-shaped relationship was seen between continuous

Table 3 Hazard ratios for primary composite outcome[a] according to alcohol consumption

	Alcohol consumption					
	Abstainers and rare	Light (<100 g/week)		Moderate (100–200 g/week)		Heavy (≥200 g/week)	
			P		P		P
HR, unadjusted (95% CI)	Ref	0.89 (0.69–1.14)	0.35	0.96 (0.67–1.40)	0.84	1.43 (1.16–1.76)	<0.01
HR, age- and sex-adjusted (95% CI)	Ref	0.83 (0.64–1.07)	0.15	0.87 (0.60–1.26)	0.45	1.28 (1.03–1.59)	0.03
HR, clinical risk factor-adjusted[b] (95% CI)	Ref	0.88 (0.68–1.13)	0.31	0.91 (0.63–1.33)	0.63	1.32 (1.06–1.66)	0.02

CI, confidence interval; HR, hazard ratio; Ref, reference.
[a]Primary composite outcome including ischaemic stroke, transient ischaemic attack, systemic embolic event, and atrial fibrillation-related hospitalization.
[b]Adjusted for age, sex, hypertension, diabetes, congestive heart failure, previous ischaemic stroke, transient ischaemic attack, vascular disease, dyslipidaemia, chronic kidney disease, cancer, and smoking status.

Table 4 Hazard ratio for adverse outcomes after propensity score matching between abstainers and rare group and heavy group

	Alcohol consumption				
	Abstainers and rare	Heavy drinkers (≥200 g/week)			
		Unadjusted		Adjusted	
		HR (95% CI)	P-Value	HR (95% CI)	P-Value
Primary composite outcome[a]	Ref	1.48 (1.14–1.91)	<0.01	1.48 (1.14–1.92)	<0.01
Secondary composite outcome 1[b]	Ref	1.43 (1.11–1.85)	0.01	1.45 (1.12–1.87)	0.01
Secondary composite outcome 2[c]	Ref	1.41 (1.10–1.81)	0.01	1.42 (1.10–1.83)	0.01
Ischaemic stroke and TIA and SEE	Ref	2.07 (0.91–4.69)	0.08	2.27 (0.99–5.19)	0.05
AF hospitalization[d]	Ref	1.39 (1.06–1.82)	0.02	1.39 (1.06–1.82)	0.02
Death	Ref	1.10 (0.26–4.61)	0.90	1.48 (0.34–6.48)	0.61
Major bleeding	Ref	1.14 (0.37–3.50)	0.81	1.15 (0.37–3.59)	0.81

AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; SEE, systemic embolic event; TIA, transient ischaemic attack.
[a]Primary composite outcome including ischaemic stroke, TIA, SEE, and AF hospitalization.
[b]Secondary composite outcome 1 including ischaemic stroke, TIA, SEE, AF hospitalization, and death.
[c]Secondary composite outcome 2 including ischaemic stroke, TIA, SEE, AF hospitalization, death, and major bleeding.
[d]AF hospitalization was defined as hospitalization for AF rate or rhythm control and heart failure management.

dose of alcohol consumption and the risk of composite adverse events of AF.

Relationship between prognosis of atrial fibrillation and alcohol consumption in previous reports

Although some prospective cohort studies have evaluated the relationship between alcohol consumption and adverse events in the AF population, the sample size was relatively small and the results were inconsistent.[10,11]

Mukamal et al. have demonstrated that habitual alcohol consumption was not associated with an increased risk of death in the Cardiovascular Health Study. In this population-based prospective cohort study with 1232 participants with documented AF during the follow-up (mean of 9.1 years), only former drinkers had a significantly increased risk of death compared with abstainers (aHR 1.27, 95% CI 1.06–1.52).[10]

In another prospective cohort study using a Danish registry, 3107 subjects (1999 men and 1108 women) who developed incident AF were categorized according to alcohol intake.[11] During a median follow-up period of 4.9 years, heavy alcohol intake was associated with a high risk of primary outcome (thromboembolism or death) compared with light-to-moderate alcohol intake (<14 drinks/week) in men (aHR 1.33, 95% CI 1.08–1.63), but not in women (aHR 1.23, 95% CI 0.78–1.96).
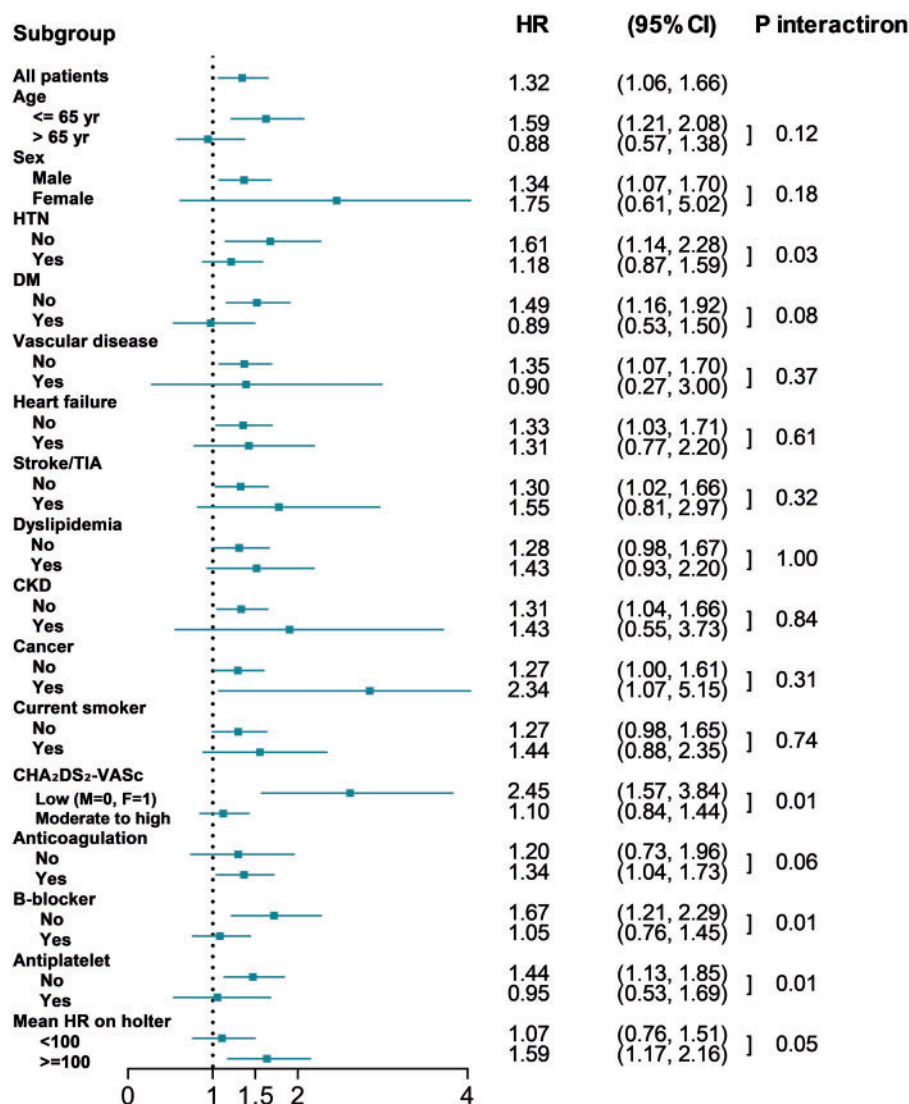
Figure 3 Subgroup analysis of primary outcome in heavy drinkers compared with the reference group (abstainers and rare drinkers). CI, confidence interval; HR, hazard ratio.

In our study, extended CV events related to AF were analysed in comparison to those in previous studies. We collected the AF-related outcomes including ischaemic stroke, TIA, SEE, or hospitalization for AF control, as well as heart failure, death, and major bleeding every 6 months in our registry only for the eligible AF population. Due to the diverse progression of AF, our extended outcomes could be more sensitive in reflecting the multiple effects of alcohol consumption on the CV system.

Our result was similar to that of a previous prospective Danish study concerning the adverse effect of heavy alcohol consumption on CV outcomes in patients with AF.[11]

J-shaped phenomenon

This study demonstrated a J-shaped association between alcohol intake and adverse events in the AF population. This was consistent with several previous studies investigating the dosing effects of alcohol consumption on CV events, including ischaemic stroke, heart failure, and death in the general population.[4,6] Many theories have been proposed for the conflicting effects according to alcohol consumption dose. Light-to-moderate alcohol consumption may be associated with increased HDL cholesterol, endothelial function, and insulin sensitivity, as well as decreased inflammation and platelet aggregation.[12–16] However, these beneficial effects of alcohol are lost with heavy consumption, which has been shown to be associated with increased oxidative stress, low HDL cholesterol, proarrhythmic effect, and other negative effects.[14,17,18] Although patients with AF are more likely to have more comorbidities than the general population, the alcohol dosing effect on the CV risk seems to be similar between the AF population and the general population. However, whether the acceptable dose of low-risk drinking for the AF population is similar to

the recommended dose for the general population (NIAAA recommended <14 drinks/week for men and 7 drinks/week for women) remains questionable, and warrants further studies.

Clinical implications

Although it is unclear whether or not light-to-moderate drinking is beneficial for the AF population, a significant effect of heavy drinking in the AF population was identified: heavy drinking was significantly associated with an increased risk of AF-related adverse events by 32% compared with the reference group. The result of this study suggests that heavy alcohol consumption should be controlled to prevent AF-related adverse events among patients with AF. Special recommendations and a warning dose level of alcohol are needed for heavy drinkers with AF. Our study showed that >135 g or about 10 drinks (one drink contains 14 g of alcohol) of weekly alcohol consumption could be harmful for the AF population.

Although the recent focus of stroke prevention in non-valvular AF is on identifying patients with a 'truly low risk' of ischaemic stroke in whom OAC has no clinical benefit, considerable number of non-anticoagulated AF patients experience unexpected ischaemic stroke. Moreover, it is unclear (with different recommendations among international guidelines) whether OAC should be prescribed in AF patient with just one risk factor (therefore would be categorized as intermediate risk with CHA_2DS_2-VASc score 1 in males and 2 in females). In this study, the association between heavy alcohol consumption and adverse event was more pronounced in patients in whom β-blockers or antiplatelets were not prescribed and in those without hypertension. This suggests that the effects of heavy drinking could be more significant in patients with AF with fewer morbidities who are generally not considered vulnerable to AF-related adverse events. The amount of alcohol consumption seems to be considered as a risk factor for stroke and adverse event in those who are generally not considered vulnerable. Further evidence is required to figure out the possibility of heavy alcohol consumption as one of the variables within stroke risk prediction models, such as the CHA_2DS_2-VASc score.

Our study failed to identify the beneficial effects of light-to-moderate drinking. It was not easy to prove the beneficial effects of alcohol as the safety margin of alcohol consumption is narrow and many confounders exist, including genetic or ethnic factors.[19,20] Many previous studies have suggested that there might be beneficial effects of alcohol on these groups, with or without significance. Further studies with large number of subjects are needed to identify special groups who will benefit from light-to-moderate drinking. However, focusing on the group with increased risk among the AF population is effective in obtaining clinical benefit by reducing adverse events.

Limitations

First, since this was a prospective observational study, its explanatory power was limited compared with randomized control trials (RCTs). However, it may be considered unethical to perform an RCT to determine the adverse effect of alcohol, particularly in patients with AF. Therefore, our prospective cohort study with almost 10 000 patients with AF has enough strength to demonstrate the real effects of chronic alcohol consumption on CV events in the AF population.

Secondly, we used the combined group of abstainers and rare drinkers (less once a month) as the reference group. Since only the abstainer group was chosen as a reference group in many previous studies, the proportion of reference group ranged from 23% to 68%, which was smaller than that in the current study.[4,6] Alcohol consumption amount of rare drinker was expected to be <10 g/week that seems to have little influence on AF prognosis, so we decided to include rare drinkers as reference group. Therefore, our reference group may rather reflect the dose effects of alcohol on CV risk in the real-world setting. We used raw groups to analyse the main result of this study, since intentionally controlling the number of groups may harm the purity of the study. To validate these large reference group comparisons, we additionally analysed the data using PS matching in a 2:1 manner to validate the multivariate analysis, and the result was similar (Table 4 and Supplementary material online, *Tables S4* and *S5*).

Thirdly, the short follow-up duration of our study (17.4 ± 7.3 months) was not enough to show significance in terms of thromboembolic events or deaths. However, thromboembolic events showed a similar J-shaped slope according to alcohol consumption as well as a marginal significance in PS matching. A longer follow-up period is needed to confirm the chronic effects of alcohol on the risk of thromboembolic events and deaths.

Finally, we did not collect information on lifetime abstainers, as it might introduce a 'sick-quitter' bias in our study. Nevertheless, the present study aimed to provide suggestions with respect to alcohol consumption for at-risk patients with AF. Hence, comparing the risk with that in contemporary non-drinkers may be more appropriate to explain the reduced risk after controlling alcohol consumption.

Conclusion

The present study suggests that heavy alcohol consumption increases the risk of AF-related adverse events in the AF population, whereas light or moderate alcohol consumption does not. This association between heavy drinking and AF-adverse events is highly significant, especially in the AF population with a low risk of stroke and fewer morbidities who are generally considered less vulnerable.

Supplementary material

Supplementary material is available at *Europace* online.

Data availability

The collected data were registered in the internet-based Clinical Research and Trial Management System (iCReaT, http://icreat.nih.go.kr); investigators can apply for use of the database.

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