

Association between body mass index and results of cryoballoon ablation in Korean patients with atrial fibrillation: an analysis from the Korean Heart Rhythm Society Cryoablation registry

Hyun Jin Ahn ^{1†}, Il-Young Oh ^{2†}, JungMin Choi ¹, Kyung-Yeon Lee ¹,
Hyo-Jeong Ahn ¹, Soonil Kwon ¹, Eue-Keun Choi ^{1,3}, Seil Oh ^{1,3},
Ju Youn Kim ⁴, Myung-Jin Cha ⁵, Chang Hee Kwon ⁶, Sung Ho Lee ⁷,
Junbeom Park ⁸, Ki-Hun Kim ⁹, Pil-Sung Yang ¹⁰, Jun-Hyung Kim ¹¹,
Jaemin Shim ¹², Hong Euy Lim ¹³, and So-Ryoung Lee ^{1,3*}

¹Department of Internal Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea; ²Cardiovascular Center, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea; ³Department of Internal Medicine, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea; ⁴Department of Internal Medicine, Heart Vascular and Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; ⁵Division of Cardiology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; ⁶Division of Cardiology, Department of Internal Medicine, Konkuk University Medical Center, Konkuk University School of Medicine, Seoul, Korea; ⁷Division of Cardiology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea; ⁸Department of Cardiology, School of Medicine, Ewha Womans University, Seoul, Korea; ⁹Department of Internal Medicine, Haeundae Paik Hospital, Inje University College of Medicine, Busan, Korea; ¹⁰Department of Cardiology, CHA Bundang Medical Center, CHA University, Seongnam, Korea; ¹¹Department of Internal Medicine, Chungnam National University Hospital, Chungnam National University College of Medicine, Daejeon, Korea; ¹²Division of Cardiology, Department of Internal Medicine, Korea University College of Medicine and Korea University Anam Hospital, Seoul, Korea; and ¹³Division of Cardiology, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Korea

Received 4 February 2024; accepted after revision 4 April 2024; online publish-ahead-of-print 16 April 2024

Aims

Pulmonary vein isolation using cryoablation is effective and safe in patients with atrial fibrillation (AF). Although both obesity and underweight are associated with a higher risk for incident AF, there is limited data on the efficacy and safety following cryoablation according to body mass index (BMI) especially in Asians.

Methods and results

Using the Korean Heart Rhythm Society Cryoablation registry, a multicentre registry of 12 tertiary hospitals, we analysed AF recurrence and procedure-related complications after cryoablation by BMI (kg/m^2) groups (BMI < 18.5, underweight, UW; 18.5–23, normal, NW; 23–25, overweight, OW; 25–30, obese I, O I; ≥ 30 , obese II, O II). A total of 2648 patients were included (median age 62.0 years; 76.7% men; 55.6% non-paroxysmal AF). Patients were categorized by BMI groups: 0.9% UW, 18.7% NW, 24.8% OW, 46.1% OI, and 9.4% OII. Underweight patients were the oldest and had least percentage of non-paroxysmal AF (33.3%). During a median follow-up of 1.7 years, atrial arrhythmia recurred in 874 (33.0%) patients (incidence rate, 18.9 per 100 person-years). After multivariable adjustment, the risk of AF recurrence was higher in UW group compared with NW group (adjusted hazard ratio, 95% confidence interval; 2.55, 1.18–5.50, $P = 0.02$). Procedure-related complications occurred in 123 (4.7%) patients, and the risk was higher for UW patients (odds ratio, 95% confidence interval; 2.90, 0.94–8.99, $P = 0.07$), mainly due to transient phrenic nerve palsy.

* Corresponding author. Tel: +82-2-2072-1864; fax: +82-2-762-9662. E-mail address: minerva1368@gmail.com

† The first two authors contributed equally to the study.

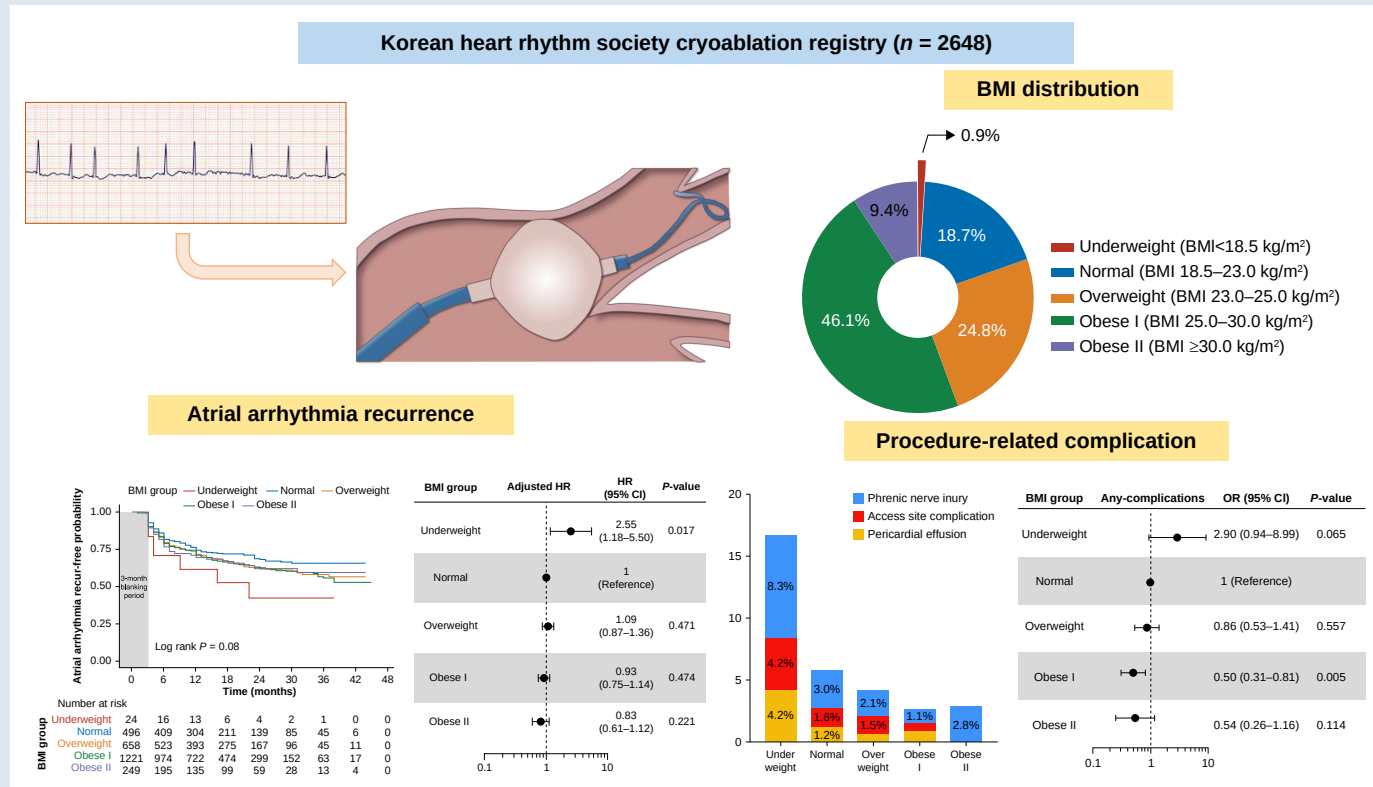
© The Author(s) 2024. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact journals.permissions@oup.com.

Conclusion

Underweight patients showed a higher risk of AF recurrence after cryoablation compared with NW patients. Also, careful attention is needed on the occurrence of phrenic nerve palsy in UW patients.

Graphical Abstract



Keywords

Atrial fibrillation • Cryoablation • Body mass index • Underweight

What's new?

- Underweight patients who undergo cryoablation for atrial fibrillation have a higher atrial arrhythmia recurrence rate compared with normal weight patients after adjusting for multivariables.
- Although procedure-related complications after cryoablation do not vary significantly among body mass index groups, caution is needed for phrenic nerve palsy in underweight groups.

Introduction

Pulmonary vein isolation (PVI) is a cornerstone catheter ablation strategy in treating patients with atrial fibrillation (AF).¹ Compared with more complex ablation strategies such as addition of linear ablation or complex fractionated atrial electrogram ablation techniques, PVI only ablation strategy has shown to be non-inferior.² In terms of PVI ablation technique, cryoballoon ablation has emerged as an alternative technique to radiofrequency (RF) ablation with study results demonstrating cryoballoon ablation to be equally advantageous and safe compared with RF ablation, for both paroxysmal and persistent AF.^{3–5}

Obesity is a well-known risk factor for incident AF,⁶ while some studies have also shown association between low body mass index (BMI)

and new-onset AF.^{7,8} Furthermore, as both underweight (UW) and extremely obese AF patients are reported to have worse clinical outcomes compared with normal weight (NW) patients, consideration of extreme BMI when diagnosing and planning treatment for AF patients is necessary.⁹ Not only has BMI been reported to be associated with AF occurrence or clinical outcome, but prior studies have also demonstrated the relationship between BMI and outcomes after AF catheter ablation. A study from China showed a U-shape relationship between BMI and AF ablation outcome, suggesting UW and obese as both associated factors with AF recurrence post-ablation,¹⁰ while BMI was not an independent risk factor for AF recurrence after catheter ablation in a different population.¹¹ These conflicting results could be due to various definitions of obesity or different selections of ablation strategy (cryoablation, RF ablation) among studies.

Given that BMI and outcome after AF ablation could be closely linked, we sought to investigate the impact of BMI on the patient characteristics, ablation efficacy, and safety in an exclusive cohort of patients receiving cryoablation for AF.

Methods

Study population

This was a retrospective analysis using the Korean Heart Rhythm Society Cryoablation registry, a multicentre registry of 12 tertiary hospitals capable

of cryoballoon ablation for AF. Patients who underwent cryoballoon ablation for drug-refractory AF were enrolled. Patients who did not have height or weight data to calculate BMI or who were lost to follow-up within a blanking period of 90 days after the ablation procedure were excluded.

This study was performed according to the Declaration of Helsinki and was exempt from review by the Seoul National University Hospital Institutional Review Board (E-2203-169-1310). The requirement for informed consent was waived because of the retrospective nature of the study. Patients' records and information were anonymized and de-identified before analysis.

Cryoballoon ablation procedure

A transeptal puncture was done for left atrial access, and a 15-F deflectable sheath (FlexCath, Medtronic) was advanced through the left atrium. A circular mapping catheter (Achieve, Medtronic) was used to record pulmonary vein potentials. Cryoenergy was delivered using exclusively the 28 mm balloon (second-generation Arctic Front Advance, Medtronic) which is the only available balloon in Korea. The cryoballoon ablation procedure generally conformed to the guidelines for cryoballoon ablation in AF, but specific approaches and dosing regimens such as energy delivery time, fluoroscopic or intracardiac echocardiographic guidance for balloon positioning and occlusion, decision of applying general anaesthesia, and post-ablation testing were decided upon the operator's discretion.

During freezing at the right pulmonary veins, continuous phrenic nerve pacing was performed using a diagnostic catheter positioned at the superior cava vein. Phrenic nerve function was monitored with palpation of diaphragmatic contraction by the physician's hand positioned at the patient's abdomen. Phrenic nerve injury was defined as transient decrease in diaphragmatic movement as confirmed by fluoroscopy or manual tactile feedback.

Definition of variable and outcome measurement

Atrial fibrillation-related clinical variables, including demographic factors, medical history, and procedure-related variables, were obtained at baseline. Age, sex, and comorbidities (hypertension, diabetes mellitus, heart failure, chronic kidney disease, hypertrophic cardiomyopathy, previous stroke/transient ischaemic attack, previous myocardial infarction) were documented, and stroke risk was calculated using the CHA₂DS₂-VASc score. Atrial fibrillation type was categorized as paroxysmal or non-paroxysmal. Transthoracic echocardiography parameters including left ventricular (LV) ejection fraction (EF), left atrial (LA) anteroposterior diameter (AP) (mm), and LA volume index (mL/m²) were measured and recorded. Patients were classified by BMI (kg/m²) groups as UW (BMI < 18.5 kg/m²), normal (NW, 18.5–23 kg/m²), overweight (OW, 23–25 kg/m²), obese I (OI, 25–30 kg/m²), or obese II (OII, ≥ 30 kg/m²) at the time of index procedure.¹²

Patients visited the hospital 2–4 weeks after discharge and underwent regular clinic follow-up at 3, 6, 9, and 12 months after ablation with 12-lead electrocardiogram (ECG). Ambulatory 24 h Holter monitoring was performed at 3 and 12 months after ablation. After the first year, follow-up was performed every 3 or 6 months by physician's discretion.

The primary endpoint was the recurrence of atrial arrhythmia which was defined as any symptomatic or asymptomatic episode of AF, atrial flutter, and/or atrial tachycardia lasting >30 s following the 90-day blanking period after cryoablation. The secondary endpoints were defined as the safety outcomes including (i) procedure-related complications which included phrenic nerve injury, access site complications (haematoma, arteriovenous fistula, or pseudoaneurysm), pericardial effusion, gastroparesis, pulmonary vein stenosis, complete atrioventricular block, haemoptysis, and atrial–oesophageal fistula and (ii) major procedure-related adverse cardiovascular events such as in-hospital myocardial infarction, stroke, and all-cause death that occurred during procedure or before discharge.

Statistical analysis

Categorical data were expressed as numbers and frequencies (percentages) and continuous data as medians with interquartile ranges (IQR) according to normality distributions. Categorical variables were compared between groups using the χ^2 test or Fisher's exact test as appropriate and continuous

variables using the Kruskal–Wallis test. Kaplan–Meier curve was used to demonstrate the cumulative incidence of clinical events according to BMI groups, and the significance level was assessed with a log-rank test. For comparison of outcomes according to BMI, multivariable Cox proportional hazard regression analysis was performed adjusting for variables that were statistically significant in univariable analysis or clinically relevant and these data were presented using hazard ratios (HRs) with the corresponding 95% confidence intervals (CIs). The following models were used: model 1 was unadjusted; model 2 was adjusted for age, sex, diabetes mellitus, hypertension, heart failure, and chronic kidney disease; model 3 was adjusted for LV EF (%), LA AP diameter (mm), and AF type (paroxysmal or non-paroxysmal) in addition to model 2. Additionally, a four-knot (5th, 35th, 65th, and 95th percentiles) restricted cubic spline (RCS) was used to present potential non-linear relationship between BMI and clinical outcomes.

All *P*-values were two-tailed, and a *P*-value of <0.05 was considered statistically significant. All statistical analyses and model development were performed using R Statistical software (version 4.2.3; R foundation for Statistical Computing, Vienna, Austria).

Sensitivity analyses

We conducted a series of sensitivity analyses to evaluate whether the observed outcomes were robust. First, since there were small number of patients and event rates in the UW group, we performed a sensitivity analysis by classifying the study population into BMI deciles (rounded to the nearest 0.5 BMI unit) to evaluate whether the findings of the primary analysis could be consistently observed with a larger sample size in the lowest BMI group. Decile group 1 represented BMI < 22.0 kg/m²; decile group 2, 22.0–23.0 kg/m²; decile group 3, 23.0–24.0 kg/m²; decile group 4, 24.0–24.5 kg/m²; decile group 5, 24.5–25.5 kg/m²; decile group 6, 25.5–26.0 kg/m²; decile group 7, 26.0–27.0 kg/m²; decile group 8, 27.0–28.0 kg/m²; decile group 9, 28.0–30.0 kg/m²; and decile group 10, ≥30.0 kg/m². Second, since obesity is defined using a lower BMI cut-off for Asian population, we performed a sensitivity analysis with BMI cut-offs according to the standardized World Health Organization (WHO) categorization¹³ (UW, BMI < 18.5 kg/m²; normal, 18.5–25.0 kg/m²; OW, 25.0–30.0 kg/m²; obesity, ≥30 kg/m²). Last, additional sensitivity analysis was performed to determine the association between BMI analysed as a continuous variable and clinical outcomes. We used the Cox proportional hazards regression model adjusting for the aforementioned variables to assess the impact of BMI on atrial arrhythmia recurrence.

Subgroup analysis

Although there is no sex-specific or age-specific standardized BMI criteria, the normal range of BMI could be distinct between sex and age groups owing to different muscle mass and fat distribution. Therefore, we performed a subgroup analysis for sex (women, men) and age (<65, ≥65), by modelling BMI as continuous variable and plotting the RCS curve in each group.

Results

A total of 2689 patients who underwent cryoballoon ablation between May 2018 and March 2023 were enrolled in this registry. One patient was excluded from this analysis because height value was missing, and 40 patients were excluded due to follow-up loss during the blanking period which led to a total of 2648 patients for analysis in this study (Figure 1). Patient distribution according to BMI as a continuous variable and as a categorical variable by the predefined BMI ranges is presented in Figure 2.

Baseline characteristics

Baseline characteristics according to BMI groups are presented in Table 1. Median age was 62.0 (IQR 56.0–68.0) years, and 2030 (76.7%) were male. Median BMI of the total study population was 25.4 (IQR 23.4–27.5) kg/m². Overall analysis comparing all BMI groups showed that patients in lower BMI groups were older (*P* < 0.001), with the UW group presenting with the oldest age [71.0 (IQR 57.5–77.0) year]. The proportion of non-paroxysmal AF was 55.6% in the total

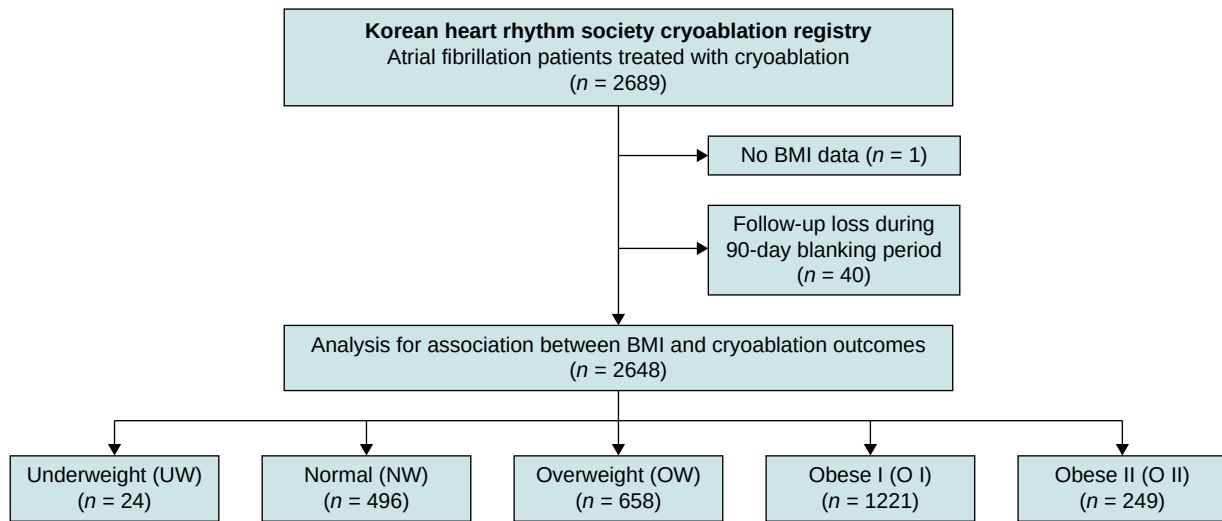
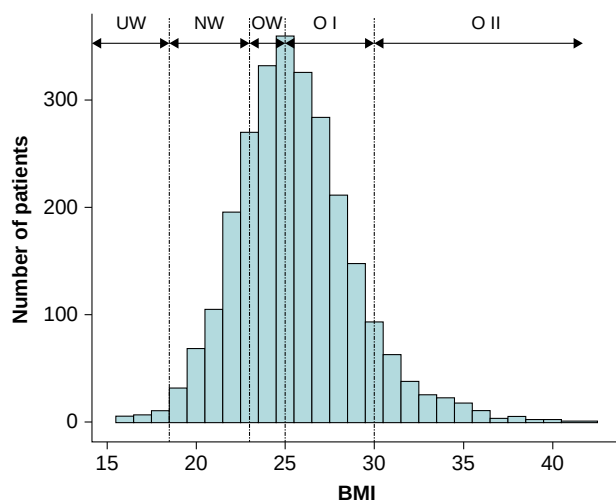


Figure 1 Study flow. BMI, body mass index.

A BMI as continuous variable



B BMI as categorical variable

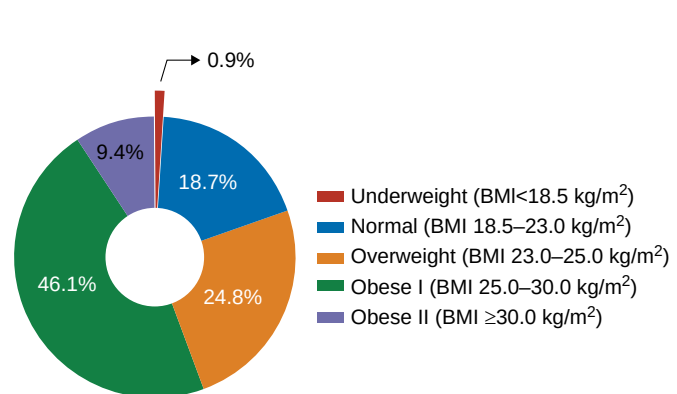


Figure 2 Patient distribution according to BMI. (A) Histogram showing patient distribution according to BMI as a continuous variable. (B) Pie chart showing patient distribution according to BMI by groups. BMI, body mass index; NW, normal weight; OW, overweight; UW, underweight.

population; the UW group showed the least proportion of non-paroxysmal AF (33.3%), while it was more prevalent with increased BMI ($P < 0.001$). Hypertension and diabetes were least prevalent in NW patients, while there was a tendency to increase in prevalence towards O II and UW bidirectionally. There were no differences between groups for history of stroke or transient ischaemic attack. Median CHA₂DS₂-VASc score was highest in the UW group [3.0 (IQR 1.0–4.0)] with no statistical significance among groups. The median LA AP diameter was 43.3 (IQR 39.0–48.0) mm, and the median LA volume index was 46.0 (IQR 37.0–58.0) mL/m² in the total population. The NW group had the smallest LA AP diameter 40.0 (IQR 36.0–45.0), mm and OW, O I, and O II patients presented with larger LA AP diameter than the NW group, with a tendency towards

progressively increased diameter size along with increased BMI. However, the UW group also showed larger diameter compared with the NW group which could be explained by older age and higher prevalence of concomitant cardiovascular diseases in this group. The baseline characteristics of patients according to BMI groups in paroxysmal and non-paroxysmal AF are described in [Supplementary material online, Tables S1 and S2](#).

Primary endpoint: recurrence of atrial arrhythmia during follow-up

During a median follow-up duration of 610 (IQR 379.0–865.5) days, the recurrence of atrial arrhythmia occurred in 874 (33.0%) patients. In the

Table 1 Baseline patient characteristics

	Total (N = 2648)	Underweight (N = 24)	Normal (N = 496)	Overweight (N = 658)	Obese I (N = 1221)	Obese II (N = 249)	P-value
Age	62.0 (56.0–68.0)	71.0 (57.5–77.0)	64.0 (58.0–70.0)	63.0 (57.0–69.0)	62.0 (55.0–67.0)	58.0 (50.0–65.0)	<0.001
Sex (male)	2030 (76.7%)	15 (62.5%)	347 (70.0%)	517 (78.6%)	971 (79.5%)	180 (72.3%)	<0.001
Non-paroxysmal AF	1473 (55.6%)	8 (33.3%)	235 (47.4%)	342 (52.0%)	716 (58.6%)	172 (69.1%)	<0.001
HTN	1521 (57.4%)	11 (45.8%)	226 (45.6%)	358 (54.4%)	735 (60.2%)	191 (76.7%)	<0.001
DM	570 (21.5%)	6 (25.0%)	85 (17.1%)	133 (20.2%)	267 (21.9%)	79 (31.7%)	<0.001
HF	625 (23.6%)	10 (41.7%)	115 (23.2%)	134 (20.4%)	294 (24.1%)	72 (28.9%)	0.015
CKD	208 (7.9%)	5 (20.8%)	57 (11.5%)	57 (8.7%)	71 (5.8%)	18 (7.2%)	<0.001
HCMP	59 (2.2%)	2 (8.3%)	12 (2.4%)	10 (1.5%)	28 (2.3%)	7 (2.8%)	0.191
Stroke/TIA	310 (11.7%)	4 (16.7%)	62 (12.5%)	85 (12.9%)	139 (11.4%)	20 (8.0%)	0.269
Previous MI	35 (1.3%)	1 (4.2%)	8 (1.6%)	11 (1.7%)	14 (1.1%)	1 (0.4%)	0.363
CHA ₂ DS ₂ -VASc	2.0 (1.0–3.0)	3.0 (1.0–4.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.141
LV EF (%)	60.0 (56.0–64.0)	60.5 (52.5–63.0)	60.0 (56.0–65.0)	60.0 (57.0–65.0)	60.0 (55.0–64.0)	59.0 (55.0–64.0)	0.012
LA AP (mm)	43.3 (39.0–48.0)	43.0 (31.6–46.0)	40.0 (36.0–45.0)	42.0 (38.0–46.5)	44.3 (40.0–49.0)	47.0 (43.0–51.0)	<0.001
LA VI (mL/m ²)	46.0 (37.0–58.0)	48.4 (40.2–72.0)	46.1 (36.3–60.4)	45.0 (36.8–56.7)	46.8 (37.4–57.8)	45.0 (37.7–60.0)	0.296

AF, atrial fibrillation; AP, anteroposterior; CKD, chronic kidney disease; DM, diabetes mellitus; EF, ejection fraction; HCMP, hypertrophic cardiomyopathy; HF, heart failure; HTN, hypertension; LA, left atrium; LV, left ventricle; MI, myocardial infarction; TIA, transient ischaemic attack; VI, volume index.
Data are presented as median (IQR) or n (%).

UW group, 11 patients (45.8%) experienced recurrence, while in the NW group, 141 patients (28.4%) experienced recurrence of atrial arrhythmia. In the OW, O I, and O II groups, the recurrence rate was 34.0%, 33.9%, and 33.7% respectively. Kaplan–Meier curve showed that the cumulative incidence of atrial arrhythmia recurrence was highest among UW patients and lowest in NW patients (Figure 3A). Supplementary material online, Figure S1, shows the cumulative incidence of atrial arrhythmia recurrence by Kaplan–Meier method at 12-, 24-, and 36-month period. The results of Cox regression models are presented in Table 2, in a stepwise manner. On univariable analysis, UW, OW, and O I patients showed higher risk of atrial arrhythmia recurrence compared with the NW patients [HR 1.93, 95% CI (1.04–3.56), $P = 0.036$; HR 1.24, 95% CI (1.01–1.53), $P = 0.045$; HR 1.25, 95% CI (1.03–1.51), $P = 0.022$, respectively]. After multivariable adjustment for comorbidities, echocardiographic parameters, and AF types, the risk of atrial arrhythmia recurrence was significantly higher only in the UW group compared with the NW group [HR 2.55, 95% CI (1.18–5.50), $P = 0.017$] (Figure 3B). The RCS for model 3 demonstrated nearly linearity association between BMI as continuous variable and atrial arrhythmia recurrence (P for non-linearity > 0.05) (Figure 3C).

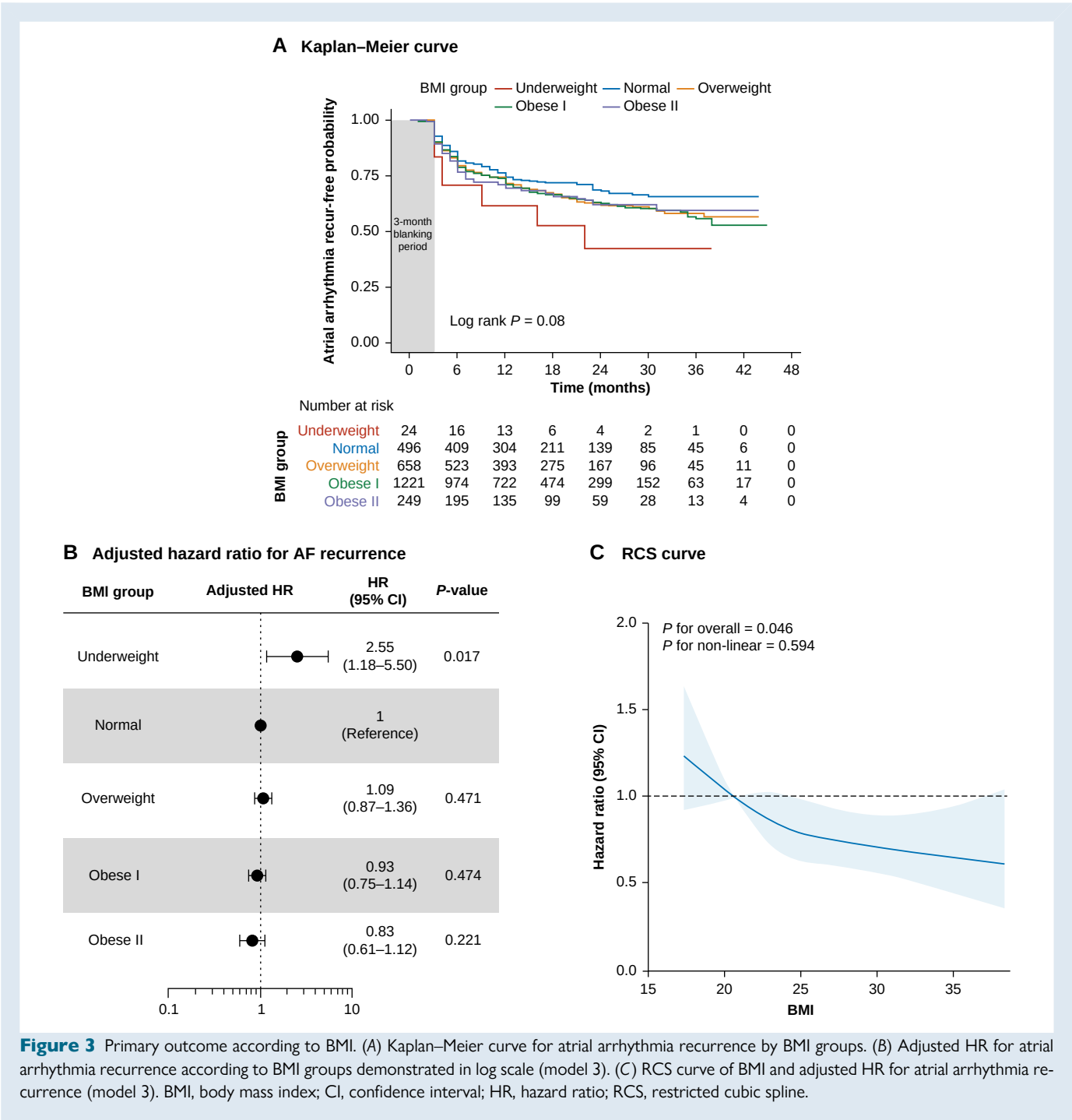
In patients with paroxysmal AF ($n = 1175$), adverse outcomes observed in UW groups were more notable after adjustment [HR 3.22, 95% CI (1.14–9.08), $P = 0.027$] compared with the UW groups in the total study population, while patients with non-paroxysmal AF showed no significant difference in outcome among BMI groups (see Supplementary material online, Tables S3 and S4 and Figure S2). Supplementary material online, Figure S3, shows the Kaplan–Meier curve for atrial arrhythmia recurrence in paroxysmal AF and non-paroxysmal AF patients according to BMI groups.

The patient characteristics by BMI deciles are presented in Supplementary material online, Table S5. Among the 10 BMI groups, decile group 2 had the lowest event rate (25.9%). With decile group 2 as the reference group, decile group 1 who represented BMI < 22.0 kg/m² showed a significantly higher risk of atrial arrhythmia recurrence after multivariable adjustment [HR 1.46, 95% CI (1.03–2.09), $P = 0.04$] (see Supplementary material online, Table S6 and Figure S4). The baseline

characteristics of patients when categorized by BMI according to the standard WHO classification is presented in Supplementary material online, Table S7. Supplementary material online, Figure S5, shows the Kaplan–Meier curves for freedom from atrial arrhythmia recurrence by WHO classification BMI ranges. Cox hazard regression analysis showed that UW patients were significantly associated with higher atrial arrhythmia recurrence compared with NW patients [HR 2.43, 95% CI (1.14–5.19), $P = 0.02$; Supplementary material online, Figure S6] which was in line with our primary analysis. When BMI was modelled as a continuous variable, BMI was negatively and independently associated with the recurrence of atrial arrhythmia after multivariable adjustment for confounders [per 5 kg/m² increase in BMI, HR 0.86, 95% CI (0.77–0.97), $P = 0.01$] (see Supplementary material online, Table S8). Overall, trends in association with the risk of atrial arrhythmia recurrence and BMI were similar in all subgroups showing higher risk of recurrence for very low BMI in both sex and age groups (see Supplementary material online, Figure S7).

Secondary endpoint: safety outcome including procedure-related complications

Any complications after cryoablation occurred in 123 (4.7%) patients: 4 UW patients (16.7%), 32 NW patients (6.5%), 37 OW patients (5.6%), 41 O I patients (3.4%), and 9 O II patients (3.6%) ($P < 0.001$) (Table 3). Compared with the NW group, the odds ratio (OR) of any complications was highest for UW patients, though not statistically significant [OR 2.90, 95% CI (0.94–8.99), $P = 0.065$] and lowest for O I patients [OR 0.50, 95% CI (0.31–0.81), $P = 0.005$] (Figure 4). Analysis employing RCS for BMI and complications indicated a nearly linear relationship (P for non-linearity > 0.05), suggesting an increased risk of complications for lower BMI (see Supplementary material online, Figure S8). Transient phrenic nerve injury was the most frequently observed acute complication (52 patients, 2.0%), and UW patients showed the highest percentage of phrenic nerve injury (8.3%), but none progressed to permanent phrenic nerve injury. Access site complication (26 patients, 1.0%) and pericardial effusion (22 patients,



0.8%) were the next common procedure-related acute complications. There was one case of pulmonary vein stenosis and no case of LA–oesophageal fistula. Major procedure-related adverse cardiovascular events were very rare in this study; in-hospital myocardial infarction occurred in one patient who was in the NW group, stroke occurred in two OW patients (0.3%) and one O I patient (0.1%), and death occurred in one patient who belonged to O I (0.1%).

Discussion

To the best of our knowledge, this is the first study to evaluate the association between BMI and outcome after cryoballoon that included a broad

range of BMI groups and is dedicated to cryoballoon technique. Our study has the following principal findings: (i) among Asian patients receiving cryoballoon, 1% were UW, 19% were NW, 25% were OW, 46% were O I, and 9% were classified as O II; (ii) the UW group was associated with a higher risk of atrial arrhythmia recurrence compared with normal BMI group after adjusting for multivariable; (iii) the results were consistent when various BMI categorical cut-offs were used and also when BMI was modelled as a continuous variable in multiple sensitivity analyses; (iv) the UW group was associated with an increased risk of acute procedure-related complications but not major procedure-related adverse cardiovascular events compared with normal BMI group.

Since cryoballoon is performed in patients who are relatively physically healthy and young compared with RF ablation, studies on the

Table 2 Cox proportional hazard regression analysis of the association between BMI and recurrence of atrial arrhythmia

	Model 1		Model 2		Model 3	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Underweight	1.93 (1.04–3.56)	0.036	1.91 (1.03–3.53)	0.039	2.55 (1.18–5.50)	0.017
Normal	1 (reference)		1 (reference)		1 (reference)	
Overweight	1.24 (1.01–1.53)	0.045	1.26 (1.02–1.56)	0.030	1.09 (0.87–1.36)	0.471
Obese I	1.25 (1.03–1.51)	0.022	1.29 (1.06–1.56)	0.012	0.93 (0.75–1.14)	0.474
Obese II	1.27 (0.97–1.66)	0.860	1.34 (1.01–1.77)	0.044	0.83 (0.61–1.12)	0.221

Model 1: unadjusted. Model 2: adjusted for age, sex, hypertension, diabetes mellitus, heart failure, and chronic kidney disease. Model 3: adjusted for age, sex, hypertension, diabetes mellitus, heart failure, chronic kidney disease, left ventricle ejection fraction, left atrium anteroposterior diameter, and AF type.
CI, confidence interval; HR, hazard ratio.

Table 3 Complication and safety issues according to BMI groups

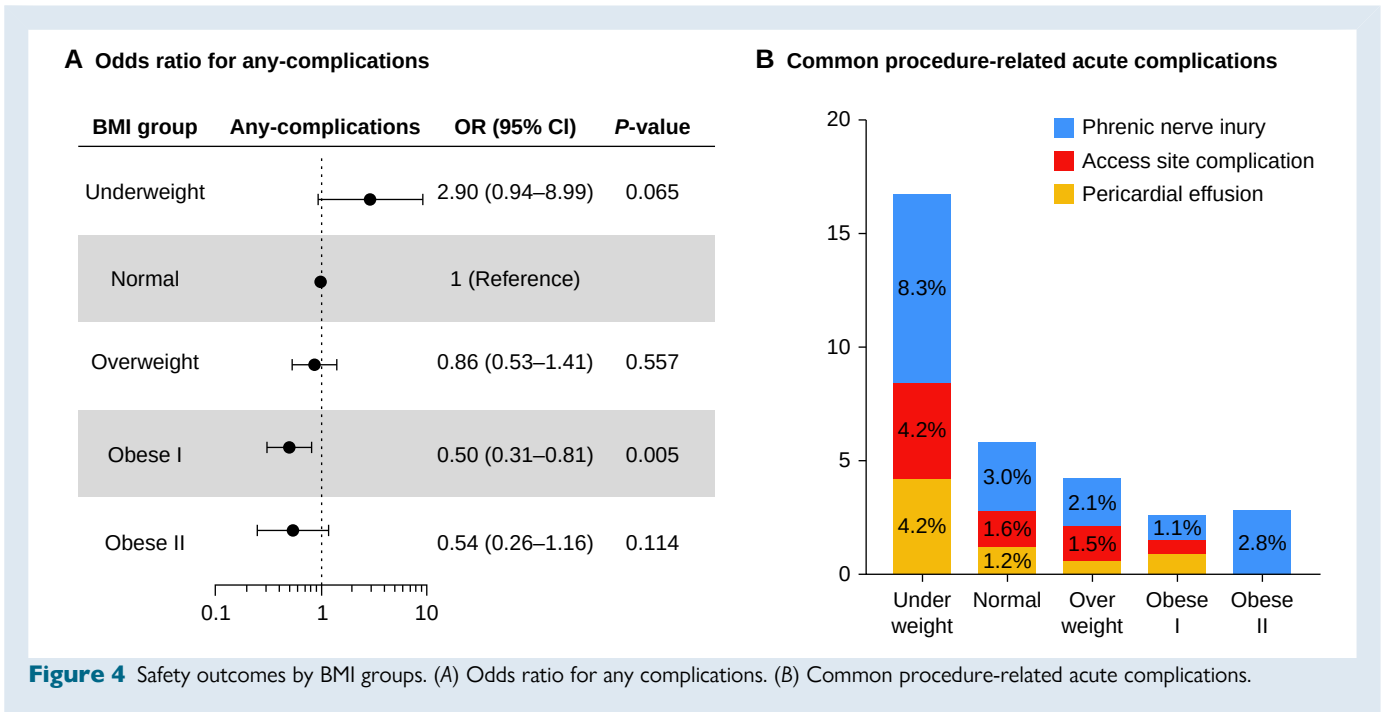
	Underweight (N = 24)	Normal (N = 496)	Overweight (N = 658)	Obese I (N = 1221)	Obese II (N = 249)	P-value
Any complication	4 (16.7%)	32 (6.5%)	37 (5.6%)	41 (3.4%)	9 (3.6%)	<0.001
Phrenic nerve injury	2 (8.3%)	15 (3.0%)	14 (2.1%)	14 (1.1%)	7 (2.8%)	0.010
Access site complication	1 (4.2%)	8 (1.6%)	10 (1.5%)	7 (0.6%)	0	0.026
Pericardial effusion	1 (4.2%)	6 (1.2%)	4 (0.6%)	11 (0.9%)	0	0.155
Gastroparesis	0	0	0	5 (0.4%)	2 (0.8%)	0.145
Pulmonary vein stenosis	0	0	1 (0.2%)	0	0	0.554
Complete AV block	0	0	1 (0.2%)	0	0	0.554
Haemoptysis	0	2 (0.4%)	6 (0.9%)	3 (0.2%)	0	0.206
In-hospital MI	0	1 (0.2%)	0	0	0	0.362
In-hospital stroke	0	0	2 (0.3%)	1 (0.1%)	0	0.543
In-hospital death	0	0	0	1 (0.1%)	0	0.883

AV, atrioventricular; BMI, body mass index; MI, myocardial infarction.
Data are presented in n (%).

association between BMI and AF recurrence are mostly focused on proving the efficacy and safety of cryoablation in patients with obesity.^{11,14} Furthermore, since these studies are mostly conducted in Caucasian patients, there is limited data on the association between UW patients and AF recurrence which is a major concern in Asians who have relatively smaller body size than Caucasians. A retrospective study from China that included four BMI categories (<18.5, 18.5–24, 25–29, and ≥30 kg/m²) indeed showed a U-shape relationship between BMI and AF ablation outcome, with both UW (<18.5 kg/m²) and obesity (≥30 kg/m²) being associated with a higher risk of AF recurrence.¹⁰ However, in the previous study, only a small number of patients (n = 74, 5.3%) received cryoablation, leading to limitation in extrapolating the result to patients undergoing cryoablation. In our study consisting of more than 2000 patients who underwent cryoablation technique, UW showed a higher risk of AF recurrence compared with NW patients after multivariable adjustment.

The reason for a higher AF recurrence in UW patients among those who received PVI with cryoablation might suggest the existence of non-PV foci contributing to AF recurrence. In a study by Inamura *et al.*,¹⁵ the authors reported lower BMI to be an independent predictor of non-PV foci for paroxysmal and persistent AF. Also, in a previous

study by Kato *et al.*,¹⁶ the authors performed high-dose isoproterenol infusion to assess the existence of non-PV foci after initial PVI using cryoablation. They revealed that lower BMI was significantly associated with non-PV foci [OR 0.95, 95% CI (0.89–1.00), *P* = 0.049] and that the existence of non-PV foci was an independent predictor of AF recurrence. Another important factor to consider in UW patients is frailty. Underweight patients in our study were older, lean, and frail patients compared with other groups. Frail state could negatively impact decisions such as antiarrhythmic drug and anticoagulation prescription in clinical practice.¹⁷ It is also associated with sarcopenia and malnutrition which could act as a substrate for AF.¹⁸ Although assessment of frailty scores was not performed in our study, the poor outcomes observed in UW patients could be in part attributed to frailty.¹⁹ Last, procedural complications such as phrenic nerve injury that immediately halts further energy delivery might increase the risk of pulmonary vein reconnection and subsequently cause higher arrhythmia recurrence.²⁰ In other words, the elevated risk of arrhythmia recurrence and phrenic nerve injury in UW patients could be relevant. However, a recent YETI subgroup analysis presented conflicting results, warranting future research to identify the optimal dosing method in cryoballoon ablation.²¹



Complications after catheter ablation occur in ~5% of patients, with most cases being vascular problems.²² In a meta-analysis that included 10 studies of patients undergoing RF ablation for AF reported that there was no significant difference in procedural complications between OW/obese and NW patients.²³ Also, a single-centre study in the United States that analysed more than 2000 patients undergoing RF ablation reported that only morbid obesity (BMI ≥ 40 kg/m²) was associated with minor complications.¹⁴ On the other hand, it is well known that cryoablation procedure requires careful consideration regarding phrenic and vagal nerve paralysis compared with RF ablation²⁴; hence, addressing this issue is crucial. In a retrospective single-centre study by Urbanek *et al.*²⁵ 600 patients with BMI ≥ 25 kg/m² who underwent cryoablation were divided into 3 groups (G1, BMI 25–29 kg/m²; G2, 30–34 kg/m²; G3, ≥35 kg/m²) and BMI had a significant impact on overall complication outcome. G3 showed the worst outcome, mainly driven by vascular access complications. There was no statistical difference in three groups regarding phrenic nerve palsy. On the contrary, in a study conducted by Malaspina *et al.*²⁶ they reported that cryoablation was safe in all groups and there was no impact of BMI on complication rate including phrenic nerve palsy or vascular complications. The patients in this study were divided into three cohorts as normal (BMI < 25 kg/m²), OW (BMI 25–30 kg/m²), and obese (BMI > 30 kg/m²). As such, previous studies regarding the association between BMI and safety outcomes of cryoablation have focused on obesity; UW patients were underrepresented, either by exclusion from study initially or combined into a single category with NW patients (BMI < 25 kg/m²).

In our study, UW patients showed a numerically higher risk of procedure-related complications compared with other BMI groups mainly owing to transient phrenic nerve injury. Transient phrenic nerve injury occurred at a higher rate in the UW group (8.3%) compared with other studies on cryoablation which report incidence of phrenic nerve injury from 1.1% to 6.2%.²⁷ Without data on temperature drop or freeze duration during cryoablation, phrenic nerve palsy cannot be thoroughly assessed, but a plausible explanation for adverse outcome in UW patients is that the thicker epicardial fat at the LA posterior wall might play as a protective role by making distance from the phrenic nerve to cryoballoon in non-UW patients.²⁶ In patients with extremely

low BMI, cryoballoon could have a higher chance of contacting the phrenic nerve, with no epicardial fat serving as a buffer.

While the primary focus of our study was to investigate the association of BMI on the clinical outcomes after cryoablation, our findings also offer valuable insights into the efficacy and safety of cryoablation technique. The 1-year cumulative incidence rate of atrial arrhythmia recurrence was 29% in our study, suggesting comparable effectiveness with contact force RF ablation.²⁸ In terms of safety, the overall complication rate (4.7%) and serious major cardiovascular events (0.2%) were very low, supporting cryoablation as a favourable modality for AF ablation. Recently, a novel cryoballoon system, the PolarX (Boston Scientific), has emerged and has shown similar efficacy with Arctic Front (Medtronic) regarding arrhythmia recurrence at 1 year after cryoablation but higher rate of transient phrenic nerve palsy.²⁹ Further investigation on the impact of BMI on safety outcomes after cryoablation using PolarX will yield valuable insights in clinical practice.

Study limitations

This study has some limitations. First, baseline information that could contribute to AF recurrence such as obstructive sleep apnoea, alcohol intake, and physical exercise were not documented. Second, data on antiarrhythmic drug use before and after the procedure were lacking and discontinuation of antiarrhythmic drugs post-ablation was decided upon the physician's discretion. Third, BMI was only collected at baseline, so BMI changes over time and the association with outcome could not be assessed. Fourth, although physicians were certified, experienced electrophysiologists as reflected by the low complication rate and recurrence rate, technical aspects and success rates could differ from physician to physician. Fifth, arrhythmia monitoring post-ablation was arbitrary and intermittent which could have led to missing the detection of AF recurrence, especially asymptomatic AF. Sixth, as BMI does not fully consider the body composition, using BMI only to define obesity could be misleading.³⁰ Previous studies have shown that the degree of abdominal adiposity is known to be associated with AF,³¹ and parameters such as waist circumference or waist-to-hip ratio are reported to be more strongly related to cardiovascular outcomes than BMI.¹⁸ Therefore, the impact of parameters of body fat and

composition (e.g. waist circumference, waist-to-hip ratio) on outcomes among patients undergoing cryoablation should be valuable to discuss, but data were not available in our study. Last, by classifying BMI according to the WHO recommendation for Asian population,¹² the UW population was relatively small compared with other groups, and therefore, the general characteristics and outcomes could have been influenced by the sample size. However, through multiple statistical analyses including BMI classification by decile, WHO standard classification, and also BMI as a continuous variable, we consistently found a higher risk of atrial arrhythmia recurrence in UW patients undergoing cryoablation.

Conclusions

In patients receiving cryoablation for AF, the UW group was associated with a significantly higher rate of atrial arrhythmia recurrence compared with the NW group, which suggests a more comprehensive understanding on the risk factors of AF recurrence in UW patients. Although cryoablation was relatively safe in UW patients, special attention for phrenic nerve palsy is necessary in these patients during procedure.

Supplementary material

Supplementary material is available at *Europace* online.

Acknowledgements

The authors would like to thank Jeong-Yoon Kim for data acquisition and ascertainment.

Funding

This study was supported by a grant from the Korean Heart Rhythm Society (KHRS 2021–3) and the Korean Cardiac Research Foundation (202103-01).

Conflict of interest: H.J.A., I.-Y.O., J.C., K.-Y.L., H.-J.A., S.K., S.O., J.Y.K., M.-J.C., C.H.K., S.H.L., J.P., K.-H.K., P.-S.Y., J.-H.K., J.S., and H.E.L.: these authors have reported that they have no relationships relevant to the contents of this paper to disclose. S.-R.L. reports speaking fees from Bayer, BMS/Pfizer, Biosense Webster, Daiichi-Sankyo, Sanofi-Aventis, Daewoong Pharmaceutical Co., Samjin Pharm, Seers Technology, Biotronik, Boston Scientific, and Medtronic and is a consultant for Biosense Webster. No fees are received personally and no fees are related to this work. E.-K.C. reports research grants or speaking fees from Abbott, Bayer, BMS/Pfizer, Biosense Webster, Chong Kun Dang, Daewoong Pharmaceutical Co., Daiichi-Sankyo, DeepQure, Dreamtech Co., Ltd, Jeil Pharmaceutical Co. Ltd, Medtronic, Samjin Pharm, Seers Technology, and SkyLabs. No fees are received personally and no fees are related to this work.

Data availability

The data set generated during and/or analysed during the current study is available from the corresponding author upon reasonable request.

References

1. Tondo C, Iacopino S, Pieragnoli P, Molon G, Verlato R, Curnis A *et al.* Pulmonary vein isolation cryoablation for patients with persistent and long-standing persistent atrial fibrillation: clinical outcomes from the real-world multicenter observational project. *Heart Rhythm* 2018;**15**:363–8.
2. Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R *et al.* Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med* 2015;**372**:1812–22.
3. Sorensen SK, Johannessen A, Worck R, Hansen ML, Hansen J. Radiofrequency versus cryoballoon catheter ablation for paroxysmal atrial fibrillation: durability of pulmonary vein isolation and effect on atrial fibrillation burden: the RACE-AF randomized controlled trial. *Circ Arrhythm Electrophysiol* 2021;**14**:e009573.
4. Shi LB, Rossvoll O, Tande P, Schuster P, Solheim E, Chen J. Cryoballoon vs. radiofrequency catheter ablation: insights from NORwegian randomized study of PERSistent Atrial Fibrillation (NO-PERSAF study). *Europace* 2022;**24**:226–33.
5. Kuck KH, Fühnkrantz A, Chun KR, Metzner A, Ouyang F, Schlüter M *et al.* Cryoballoon or radiofrequency ablation for symptomatic paroxysmal atrial fibrillation: reintervention, rehospitalization, and quality-of-life outcomes in the FIRE AND ICE trial. *Eur Heart J* 2016;**37**:2858–65.
6. Goudis CA, Korantzopoulos P, Ntalas IV, Kallergis EM, Ketikoglou DG. Obesity and atrial fibrillation: a comprehensive review of the pathophysiological mechanisms and links. *J Cardiol* 2015;**66**:361–9.
7. Kang SH, Choi EK, Han KD, Lee SR, Lim WH, Cha MJ *et al.* Underweight is a risk factor for atrial fibrillation: a nationwide population-based study. *Int J Cardiol* 2016;**215**:449–56.
8. Hsu JC, Yang YY, Chuang SL, Chung YW, Wang CH, Lin LY. Underweight is a major risk factor for atrial fibrillation in Asian people with type 2 diabetes mellitus. *Cardiovasc Diabetol* 2021;**20**:226.
9. Camm CF, Virdone S, Goto S, Bassand J-P, van Eickels M, Haas S *et al.* Association of body mass index with outcomes in patients with newly diagnosed atrial fibrillation: GARFIELD-AF. *Open Heart* 2022;**9**:e002038.
10. Deng H, Shantsila A, Guo P, Potpara TS, Zhan X, Fang X *et al.* A U-shaped relationship of body mass index on atrial fibrillation recurrence post ablation: a report from the Guangzhou atrial fibrillation ablation registry. *EBioMedicine* 2018;**35**:40–5.
11. Letsas KP, Siklody CH, Korantzopoulos P, Weber R, Bürkle G, Mihos CC *et al.* The impact of body mass index on the efficacy and safety of catheter ablation of atrial fibrillation. *Int J Cardiol* 2013;**164**:94–8.
12. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004;**363**:157–63.
13. Flegal KM, Kit BK, Graubard BI. Body mass index categories in observational studies of weight and risk of death. *Am J Epidemiol* 2014;**180**:288–96.
14. Winkle RA, Mead RH, Engel G, Kong MH, Fleming W, Salcedo J *et al.* Impact of obesity on atrial fibrillation ablation: patient characteristics, long-term outcomes, and complications. *Heart Rhythm* 2017;**14**:819–27.
15. Inamura Y, Nitta J, Inaba O, Sato A, Takamiya T, Murata K *et al.* Presence of non-pulmonary vein foci in patients with atrial fibrillation undergoing standard ablation of pulmonary vein isolation: clinical characteristics and long-term ablation outcome. *Int J Cardiol Heart Vasc* 2021;**32**:100717.
16. Kato N, Nitta J, Sato A, Inamura Y, Takamiya T, Inaba O *et al.* Characteristics of the non-pulmonary vein foci induced after second-generation cryoballoon ablation for paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol* 2020;**31**:174–84.
17. Savelieva I, Fumagalli S, Kenny RA, Anker S, Benetos A, Boriani G *et al.* EHRA expert consensus document on the management of arrhythmias in frailty syndrome, endorsed by the Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA). *Europace* 2023;**25**:1249–76.
18. Ahn HJ, Lee SR, Choi EK, Han KD, Rhee TM, Kwon S *et al.* Associations between obesity parameters and the risk of incident atrial fibrillation and ischaemic stroke in the different age groups. *Front Cardiovasc Med* 2022;**9**:906844.
19. Dulai R, Uy CP, Sulke N, Patel N, Veasey RA. A retrospective analysis of frailty status on atrial fibrillation catheter ablation outcomes. *Pacing Clin Electrophysiol* 2023;**46**:855–60.
20. Heeger CH, Popescu SS, Saraei R, Kirstein B, Hatahet S, Samara O *et al.* Individualized or fixed approach to pulmonary vein isolation utilizing the fourth-generation cryoballoon in patients with paroxysmal atrial fibrillation: the randomized INDI-FREEZE trial. *Europace* 2022;**24**:921–7.
21. Heeger CH, Popescu S, Sohns C, Pott A, Metzner A, Inaba O *et al.* Impact of cryoballoon application abortion due to phrenic nerve injury on reconnection rates: a YETI subgroup analysis. *Europace* 2023;**25**:374–81.
22. Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyue JY, Cronin EM *et al.* 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2024;**83**:109–279.
23. Liu M, Mei K, Liu X, Zhao Y. Impact of body mass index on procedural complications, procedure duration, and radiation dose in patients with atrial fibrillation undergoing radiofrequency ablation: a systematic review and meta-analysis. *Clin Cardiol* 2020;**43**:1067–75.
24. Steinbeck G, Sinner MF, Lutz M, Müller-Nurasyid M, Käb S, Reinecke H. Incidence of complications related to catheter ablation of atrial fibrillation and atrial flutter: a nationwide in-hospital analysis of administrative data for Germany in 2014. *Eur Heart J* 2018;**39**:4020–9.
25. Urbanek L, Bordignon S, Chen S, Bologna F, Tohoku S, Dincher M *et al.* Impact of body mass index on cryoablation of atrial fibrillation: patient characteristics, procedural data, and long-term outcomes. *J Cardiovasc Electrophysiol* 2022;**33**:1106–15.
26. Malaspina D, Brasca F, Iacopino S, Arena G, Molon G, Pieragnoli P *et al.* Cryoablation for pulmonary veins isolation in obese patients with atrial fibrillation compared to nonobese patients. *Pacing Clin Electrophysiol* 2021;**44**:306–17.
27. Heeger CH, Sohns C, Pott A, Metzner A, Inaba O, Straube F *et al.* Phrenic nerve injury during cryoballoon-based pulmonary vein isolation: results of the worldwide YETI registry. *Circ Arrhythm Electrophysiol* 2022;**15**:e010516.

28. Shurrab M, Di Biase L, Briceno DF, Kaoutskaia A, Haj-Yahia S, Newman D et al. Impact of contact force technology on atrial fibrillation ablation: a meta-analysis. *J Am Heart Assoc* 2015;**4**:e002476.
29. Tanese N, Almorad A, Pannone L, Defaye P, Jacob S, Kilani MB et al. Outcomes after cryoballoon ablation of paroxysmal atrial fibrillation with the PolarX or the Arctic Front Advance Pro: a prospective multicentre experience. *Europace* 2023;**25**:873–9.
30. Li YG, Xie PX, Alsheikh-Ali AA, AlMahmeed W, Sulaiman K, Asaad N et al. The “obesity paradox” in patients with atrial fibrillation: insights from the Gulf SAFE registry. *Front Cardiovasc Med* 2022;**9**:1032633.
31. Aune D, Sen A, Schlesinger S, Norat T, Janszky I, Romundstad P et al. Body mass index, abdominal fatness, fat mass and the risk of atrial fibrillation: a systematic review and dose-response meta-analysis of prospective studies. *Eur J Epidemiol* 2017;**32**:181–92.