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ORIGINAL ARTICLE

Effect of Semaglutide on Atrial Arrhythmias Recurrence Following Ablation for Atrial Fibrillation: A Prospective Study

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BACKGROUND: Recurrence of atrial arrhythmias remains a significant challenge following catheter ablation for atrial fibrillation. The potential role of semaglutide in reducing atrial arrhythmia recurrence postablation is unclear.

METHODS: A consecutive sample of 437 patients with a body mass index ≥24 kg/m² and type 2 diabetes who underwent their first atrial fibrillation ablation procedure between January 2022 and March 2024 were enrolled. Participants were divided into a semaglutide group and a control group based on patient preference. The primary outcome was the freedom from atrial arrhythmia recurrence during the 12-month follow-up period after the 3-month blanking period postablation.

RESULTS: Of the 437 enrolled patients, 158 opted for semaglutide therapy and 279 declined. At baseline, the semaglutide group had higher body mass index (27.5 [2.2] versus 27.0 [2.4]; P=0.038) and glycated hemoglobin levels (8.0 [1.0] versus 7.6 [1.1]; P<0.001) compared with controls. During the 12-month follow-up, the semaglutide group showed a higher event-free rate for recurrent atrial arrhythmias (hazard ratio, 0.68 [95% CI, 0.49–0.95]; P=0.030), greater weight loss (−8.2% [3.2] versus −4.6% [2.9]; P<0.001), and larger reductions in glycated hemoglobin (−1.3% [0.8] versus −0.6% [0.8]; P<0.001).

CONCLUSIONS: Semaglutide treatment following catheter ablation for atrial fibrillation is associated with a lower rate of atrial arrhythmia recurrence over 12 months and may lead to improvements in weight and glycated hemoglobin levels.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: atrial fibrillation ■ body mass index ■ catheter ablation ■ glycated hemoglobin ■ semaglutide

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Catheter ablation is an effective treatment for atrial fibrillation (AF), offering significant clinical benefits in symptom relief, quality of life improvement, and reduction in AF burden.[1–4] Despite its efficacy, AF recurrence remains a major challenge following catheter ablation.[5]

The global rise in overweight and obesity has become a significant public health concern. In China, the prevalence of overweight and obesity among adults aged 18 years and older is 34.3% and 16.4%, respectively, whereas in the United States, adult obesity rates exceed 35%.[6] Weight reduction through lifestyle modifications has been associated with a decreased risk of AF recurrence postablation.[7–9] Both the American College of Cardiology and the European Society of Cardiology guidelines emphasize weight reduction as a critical intervention to

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WHAT IS KNOWN?

- Recurrence of atrial arrhythmias remains a significant challenge following catheter ablation for atrial fibrillation.
- Semaglutide, a glucagon-like peptide 1 receptor agonist, has been shown to improve obesity and type 2 diabetes, but its role in reducing atrial arrhythmia recurrence postablation is unclear.

WHAT THE STUDY ADDS

- In this prospective study, semaglutide use was associated with a higher event-free rate for recurrent atrial arrhythmias over 12 months following catheter ablation.
- Semaglutide therapy postablation may lead to weight loss and greater reductions in glycated hemoglobin levels
- Semaglutide may serve as a therapeutic option to reduce arrhythmia recurrence and improve metabolic outcomes in patients with atrial fibrillation, overweight, and type 2 diabetes.
- Randomized prospective trials are needed to demonstrate the generalizability of the effect.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
BMI	body mass index
CaMKII	calcium/calmodulin-dependent protein kinase II
DPP-4	dipeptidyl peptidase 4
GLP-1 RAs	glucagon-like peptide-1 receptor agonists
HR	hazard ratio
NCX	sodium-calcium exchanger
PKA	protein kinase A
SGLT-2	sodium-glucose cotransporter 2

reduce AF burden and recurrence in overweight and obese populations.[10,11] However, achieving sustained weight loss is challenging due to factors such as patient motivation, physical capacity, and dietary habits, making consistent and reproducible weight management strategies difficult to implement, particularly in overweight or obese individuals.[10,11] Additionally, diabetes and elevated glycated hemoglobin levels have been linked to prolonged hospitalization and increased AF recurrence rates after catheter ablation.[12–15] Optimal glycemic control has shown potential benefits in alleviating AF-related symptoms, reducing disease burden, reversing AF phenotype (from persistent to paroxysmal or AF-free status), and promoting sinus rhythm maintenance.[16,17]

GLP-1 RAs (glucagon-like peptide 1 receptor agonists), such as semaglutide, have recently demonstrated significant efficacy in the management of obesity and type 2 diabetes, with additional benefits in improving cardiovascular outcomes.[18–20] These properties make GLP-1 RAs a promising therapeutic strategy for patients with AF, particularly those with metabolic comorbidities. However, evidence on the impact of GLP-1 RAs on AF recurrence remains inconsistent, with conflicting results from retrospective studies and a lack of high-quality prospective data.[5,21–24]

Therefore, this study aims to evaluate the effects of semaglutide on atrial arrhythmia recurrence, weight control, and glycemic management in patients with AF undergoing catheter ablation.

METHODS

Study Design

This is a prospective study conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent. The study was approved by the Ethics Committee of Shanghai Chest Hospital. The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Participants

A total of 437 patients who underwent their first AF ablation procedure across 4 centers from January 2022 to March 2024 and were willing to adopt lifestyle interventions following nutrition counseling were enrolled. All participants had a body mass index (BMI) ≥24 kg/m^2 and type 2 diabetes. Although all patients were advised to receive subcutaneous semaglutide therapy (1.0 mg weekly), 158 patients consented to the treatment.

Inclusion Criteria

The criteria for inclusion are as follows: (1) age >18 years; (2) symptomatic AF refractory or intolerant to at least 1 class I or class III antiarrhythmic drug; (3) diagnosed with type 2 diabetes; (4) BMI ≥24 kg/m^2; and (5) capable of understanding the study's objectives, voluntarily consenting to participate, and signing the informed consent form.

Exclusion Criteria

The criteria for exclusion are as follows: (1) permanent AF; (2) history of acute coronary events or percutaneous coronary intervention within 6 months before enrollment; (3) history of stroke or transient ischemic attack within 6 months before enrollment; (4) pregnant or breastfeeding women, or women planning pregnancy; (5) patients with a clear bleeding tendency who cannot receive postoperative anticoagulation; (6) contraindications to antidiabetic drugs, including GLP-1 RAs; (7) unable to engage in physical exercise due to illness or disability; (8) life expectancy <12 months; and (9) patients with psychiatric disorders or mental health issues.

Ablation and Treatment

All patients underwent pulmonary vein isolation, with the electrophysiological end point of pulmonary vein isolation being bidirectional conduction block between the left atrium and

pulmonary veins. Additional ablation techniques (including linear ablation, Marshall vein alcohol ablation, rotor ablation, etc) were allowed at the discretion of the operator.

Semaglutide Group

Participants received standard postablation care, including antiarrhythmic and anticoagulation therapy, along with subcutaneous semaglutide injections added to their general glucose-lowering regimen. Semaglutide injections were started within 48 hours postablation, administered at any time of the day, regardless of meals, and could be self-injected in the thigh, abdomen, or upper arm. Injections were to be done on the same day of the week. The semaglutide regimen followed a fixed dose escalation protocol, with the dose doubling every 4 weeks, starting at 0.25 mg and increasing up to a maintenance dose of 1.0 mg after reaching the target dose.

Lifestyle Intervention Group

This group received standard postablation care, including antiarrhythmic and anticoagulation therapy. Both groups received structured weight management lifestyle interventions according to current clinical guidelines, including dietary control and physical activity. Both groups discontinued the use of antiarrhythmic medications at 3 months postoperatively.

Outcomes

The primary end point of this study was the freedom from atrial arrhythmia recurrence during the 12-month period after the 3-month blanking period following catheter ablation, with recurrence defined as the occurrence of atrial arrhythmias lasting ≥30 seconds, including AF, atrial flutter, or atrial tachycardia. Secondary end points included the freedom from AF recurrence during the 12-month period after the 3-month blanking period following catheter ablation, percentage of weight loss at 12 months, changes in glycated hemoglobin levels, and changes in New York Heart Association classification. Safety and tolerability were assessed based on adverse events, including procedure-related adverse events (such as cardiac tamponade/perforation, major vascular access complications/bleeding, pericarditis, stroke/cerebrovascular accident, transient ischemic attack, and postprocedural fever) and semaglutide-related adverse events (such as gastrointestinal symptoms, nausea, diarrhea, constipation, vomiting, decreased appetite, adverse events leading to premature treatment discontinuation, hepatic events, injection-site reactions, allergic reactions, hypoglycemic episodes, acute pancreatitis, and thyroid disease).

Follow-Up and Data Collection

Participants were evaluated at 1, 3, 6, 9, and 12 months to assess clinical outcomes, including the recurrence of atrial arrhythmias, weight changes, and glycemic control. At each follow-up visit, ECG and 24-hour Holter monitoring were performed. Physicians were permitted to conduct remote follow-ups, with assessments of atrial arrhythmias based on patient self-reports of symptoms (eg, palpitations), electrocardiograms recorded during episodes, 24-hour Holter monitoring, single-lead ECG patches, or data from wearable devices such as smartwatches (Supplemental Method 1). During each follow-up, adherence to semaglutide therapy and lifestyle interventions was documented (Supplemental Method 2). Additionally, adverse events associated with semaglutide therapy were closely monitored, with particular focus on hypoglycemia, pancreatitis, gastrointestinal adverse events leading to treatment discontinuation, and other serious side effects.

Statistical Analysis

Continuous variables were compared using the Student *t* test or the Wilcoxon rank-sum test, depending on the distribution of the data. Categorical variables were analyzed with the χ^2 test. The event-free rate was estimated using the Kaplan-Meier method, and differences were assessed using the log-rank test. Variables with $P<0.10$ in univariable screening and prespecified clinically significant covariates were entered into the multivariable Cox proportional hazard model. The primary outcome analysis of this study excluded participants lost to follow-up, whereas sensitivity analysis 1 also removed this population. In sensitivity analysis 2, both intention-to-treat and per-protocol set analyses were conducted, including best-case scenario, worst-case scenario, and multiple imputation (multivariable imputation by chained equations) outcomes for the lost-to-follow-up population. Sensitivity analysis 3 performed an on-treatment analysis. The sensitivity analysis was conducted based on model 1, with adjustments made for the use of antiarrhythmic drugs, antidiabetic drugs, and baseline prevalent conditions, including hypertension, coronary heart disease, stroke, obstructive sleep apnea, and congestive heart failure. Statistical analyses were performed using SPSS 26.0 (IBM Corp, Armonk, NY) and R 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Graphs were created using GraphPad Prism 9 (GraphPad Software Inc, San Diego, CA). All statistical tests were 2-tailed, and a *P* value of <0.05 was considered statistically significant.

RESULT

Study Population

Between January 2022 and March 2024, 437 patients from 4 centers were enrolled. Of these, 158 patients who opted for semaglutide therapy were assigned to the semaglutide group, whereas 279 patients who declined semaglutide treatment were allocated to the lifestyle intervention group. During follow-up, 28 patients (10.03%) in the semaglutide group and 12 patients (7.59%) in the lifestyle intervention group were lost to follow-up. A total of 398 participants (91.07%) completed the study, with detailed information provided in Figure 1. Final follow-up was conducted in March 2025.

Baseline Characteristics

The study included 289 (66.1%) males and 290 (66.4%) patients with persistent AF. At baseline, the semaglutide group had higher BMI (mean [SD], 27.5 [2.2] versus 27.0 [2.4]; $P=0.038$) and glycated hemoglobin (8.0% [1.0] versus 7.6% [1.1]; $P<0.001$) compared with the control group. No significant differences were observed in age,

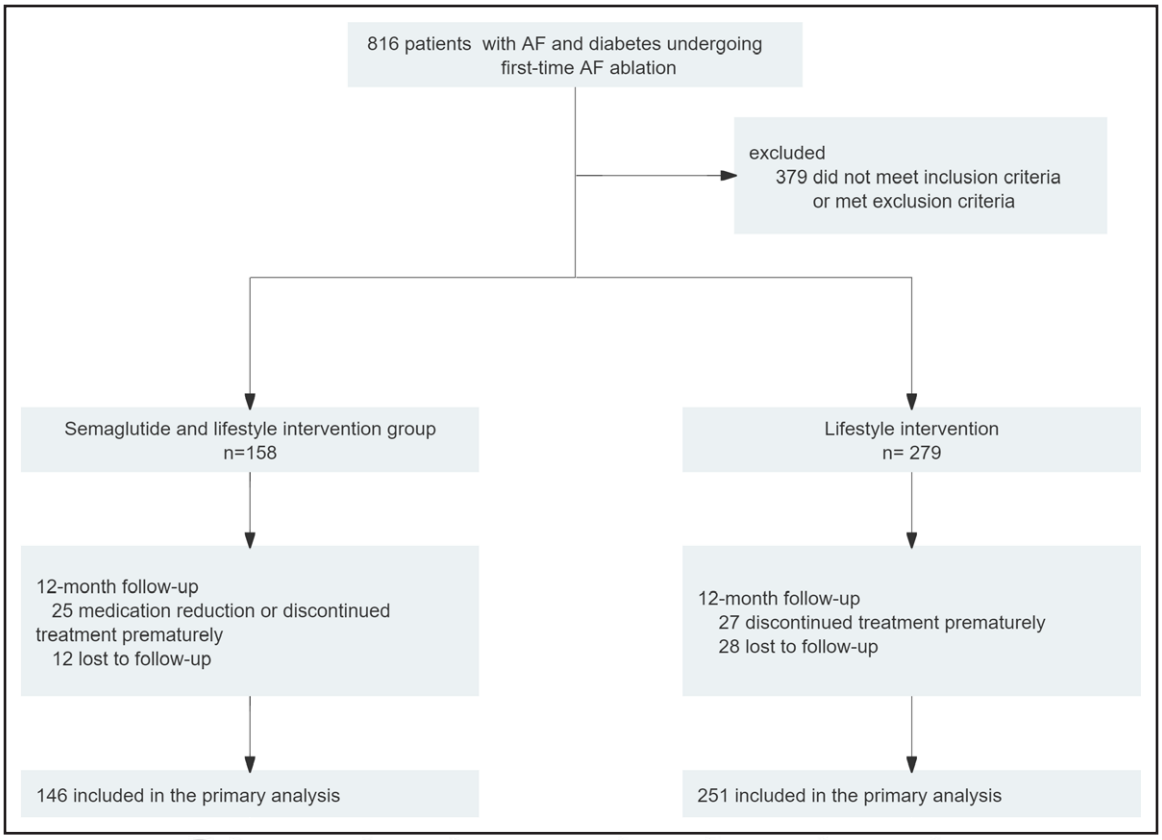

Figure 1. Flowchart.
AF indicates atrial fibrillation.

sex, medical history, left atrium dimension, left ventricular ejection fraction, or antiarrhythmic drug use. Metformin (47.5% versus 34.4%; *P*=0.007) and insulin (20.9% versus 13.3%; *P*=0.037) use differed significantly between groups, while other antidiabetic medications showed no differences (*P*>0.05; Table 1). All patients underwent successful ablation, with no procedural differences between groups (*P*>0.05; Table S1).

Primary Outcomes

Among the 397 study completers, 36 patients (9.1%) underwent continuous monitoring by a wearable device, whereas 361 (90.9%) received intermittent monitoring. At 12 months, patients in the semaglutide group showed a higher event-free survival rate for recurrent atrial arrhythmias compared with those in the lifestyle intervention group (hazard ratio [HR], 0.68 [95% CI, 0.49–0.95]; log-rank *P*=0.030; Figure 2A).

Secondary Outcomes

At 12 months postablation, patients in the semaglutide group had a higher event-free survival rate for recurrent AF compared with those in the lifestyle intervention group (HR, 0.63 [95% CI, 0.45–0.91]; log-rank *P*=0.019; Figure 2B). Weight loss was greater in the semaglutide group (mean [SD], −6.2 kg [2.6] versus −3.4 kg [2.2]; *P*<0.001; percentage change, −8.2% [3.2] versus −4.6% [2.9]; *P*<0.001; Table 2; Figure S1). Glycated hemoglobin reduction was also more significant in the semaglutide group (6.7% [0.8] versus 7.0% [1.0]; *P*<0.001; Table 2). No differences were observed in antiarrhythmic drug use (16% versus 19%; *P*=0.566) or New York Heart Association classification (*P*=0.207) between groups at 12 months (Table 2; Tables S4 and S5).

Subgroup Analysis

Subgroup analysis by AF type showed no significant differences in freedom from atrial arrhythmia recurrence (paroxysmal AF: log-rank *P*=0.164; persistent AF: log-rank *P*=0.136) or AF recurrence (paroxysmal AF: log-rank *P*=0.054; persistent AF: log-rank *P*=0.173; Figure S2). In patients with BMI <27 kg/m^2, no significant differences were observed in freedom from atrial arrhythmia recurrence (log-rank *P*=0.162) or AF recurrence (log-rank *P*=0.078; Figure S3A and S3B). However, in patients with BMI ≥27 kg/m^2, the semaglutide group had a lower risk of freedom from atrial arrhythmia recurrence (HR, 0.64 [95% CI, 0.41–0.99]; log-rank *P*=0.043) and

Table 1. Baseline Characteristics of the Study Population

Characteristic	Control group (n=279)	Treatment group (n=158)	*P* value
Age, mean (SD), y	68.6 (8.1)	67.3 (8.9)	0.111
Male	186 (66.7)	103 (65.2)	0.754
Body mass index, mean (SD), kg/m^2	27.0 (2.4)	27.5 (2.19)	0.038
Persistent AF	193 (69.2)	97 (61.4)	0.098
CHA_2DS_2-VASc score, median (IQR)	3.0 (3.0–4.5)	3.0 (2.3–4.0)	0.466
AF history, mean (SD), m	8.0 (1.0–36.0)	12.0 (1.0–36.0)	0.649
NYHA class			0.610
I	18 (6.5)	11 (7.0)	
II	212 (76.0)	125 (79.1)	
III	49 (17.6)	22 (13.9)	
Hypertension	211 (75.6)	114 (72.1)	0.424
Coronary heart disease	67 (24.0)	32 (20.2)	0.367
Stroke	44 (15.8)	30 (19.0)	0.389
Congestive heart failure	32 (11.5)	22 (13.9)	0.454
Obstructive sleep apnea	23 (8.24)	17 (10.76)	0.381
Glycated hemoglobin, mean (SD), %	7.6 (1.1)	8.0 (1.0)	<0.001
Left atrial diameter, mean (SD), mm	42.91 (5.44)	42.05 (5.36)	0.113
LVEF, mean (SD), %	61.1 (6.9)	60.9 (7.1)	0.723
Mitral regurgitation			0.653
No	82 (29.4)	54 (34.2)	
Mild	173 (62.0)	89 (56.3)	
Moderate	21 (7.5)	14 (8.9)	
Severe	3 (1.1)	1 (0.6)	
Tricuspid regurgitation			0.093
No	130 (46.6)	85 (53.8)	
Mild	119 (42.7)	53 (33.5)	
Moderate	26 (9.3)	20 (12.7)	
Severe	4 (1.4)	0 (0.0)	
Amiodarone	187 (67.0)	100 (63.3)	0.430
Propafenone	23 (8.2)	20 (12.7)	0.137
Dronedarone	9 (3.2)	11 (7.0)	0.073
Beta blockers	67 (24.0)	31 (19.6)	0.290
Metformin	96 (34.4)	75 (47.5)	0.007
SGLT-2 inhibitors	34 (12.2)	29 (18.4)	0.078
DPP-4 inhibitors	37 (13.3)	27 (17.1)	0.277
Insulin	37 (13.3)	33 (20.9)	0.037
α-glucosidase inhibitors	60 (21.5)	40 (25.3)	0.362
Sulfonylureas	30 (10.8)	26 (16.5)	0.087
Thiazolidinediones	22 (7.9)	10 (6.3)	0.549

Values are mean (SD), n (%), or median (IQR). AF indicates atrial fibrillation; DPP-4, dipeptidyl peptidase 4; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; and SGLT-2, sodium-glucose cotransporter 2.

AF recurrence (HR, 0.62 [95% CI, 0.39–0.98]; log-rank *P*=0.043; Figure S3C and S3D).

Adverse Clinical Outcomes

A total of 437 patients (158 in the semaglutide group and 279 in the lifestyle intervention group) were included in the procedure–related safety analysis. In the lifestyle intervention group, there was 1 case of cardiac tamponade/perforation, 4 cases of major vascular access complications/bleeding, and 6 cases of postprocedural fever. No cases of pericarditis, stroke/cerebrovascular accidents, or transient ischemic attacks were reported. In the semaglutide group,

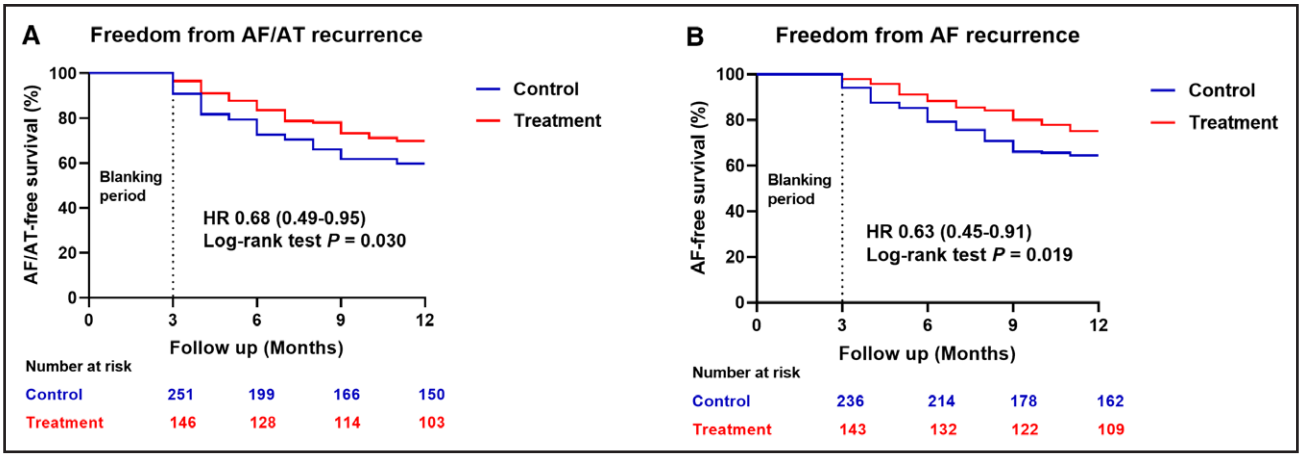

Figure 2. Kaplan-Meier curve analysis.
A, Kaplan-Meier curve for freedom from atrial arrhythmia recurrence. **B**, Kaplan-Meier curves for freedom from atrial fibrillation (AF) recurrence. AT indicates atrial tachycardia; and HR, hazard ratio.

there were 5 cases of major vascular access complications/bleeding and 3 cases of postprocedural fever. No cases of cardiac tamponade/perforation, stroke/cerebrovascular accident, or pericarditis occurred (Table S2).

Regarding semaglutide-related adverse events, in the semaglutide group, 64 patients (43.83%) reported digestive tract symptoms. The majority of these symptoms were mild in severity and tended to diminish over time. Seventeen patients (11.6%) experienced adverse events

Table 2. Outcomes

Outcomes	Control (n=251)	Treatment (n=146)	HR (95% CI)	*P* value
Rhythm outcome, n (%)				
Freedom from AF/AT recurrence at 12 m	101 (40.2)	44 (30.1)	0.68 (0.49–0.95)	0.030
Freedom from AF recurrence at 12 m	89 (35.5)	36 (24.7)	0.63 (0.45–0.91)	0.019
Bodyweight outcomes				
Weight changes at 12 m, kg	−3.4 (2.2)	−6.2 (2.6)		<0.001
Weight reduction percentage at 12 m	−4.6 (2.9)	−8.2 (3.2)		<0.001
≥5% weight reduction at 12 m	97 (38.6)	108 (73.9)		<0.001
≥10% weight reduction at 12 m	13 (5.2)	38 (25.0)		<0.001
Glycated hemoglobin, %				
Glycated hemoglobin at baseline	7.7 (1.2)	8.0 (1.0)		0.008
Glycated hemoglobin at 12 m	7.0 (1.0)	6.7 (0.8)		<0.001
Change from baseline to 12 m	−0.6 (0.8)	−1.3 (0.8)		<0.001
AAD use, n (%)				
AAD use at baseline	198 (78.9)	119 (81.5)		0.530
AAD use at 12 m	47 (18.7)	24 (16.4)		0.566
NYHA class, n (%)				
At baseline				0.825
I	18 (7.2)	11 (7.53)		
II	191 (76.1)	114 (78.1)		
III	42 (16.7)	21 (14.4)		
At 12 m				0.207
I	72 (28.7)	52 (35.6)		
II	143 (57.0)	80 (54.8)		
III	36 (14.3)	14 (9.6)		

Values are mean (SD) or n (%). AAD indicates antiarrhythmic drugs; AF, atrial fibrillation; AT, atrial tachycardia; HR, hazard ratio; and NYHA, New York Heart Association.

leading to premature discontinuation of treatment, including 10 cases of severe digestive tract symptoms, 1 case of allergic reactions, 4 cases of hypoglycemic episodes, and 2 cases of hepatic events. Eight patients stopped treatment for reasons unrelated to adverse events (eg, personal choice, nonmedical factors). No cases of pancreatitis or thyroid tumors were reported (Table S3).

Cox Regression Analyses

Variables potentially associated with freedom from atrial arrhythmia recurrence were first assessed using univariable Cox analysis. Those with a $P<0.10$ were included in a multivariable Cox regression model. Semaglutide demonstrated a statistically significant protective effect against atrial arrhythmia recurrence (HR, 0.66 [95% CI, 0.46–0.95];$P=0.025$) in the adjusted analysis (Table 3).

Stratified Analyses

Subgroup analyses based on age, gender, AF type, AF history, BMI, glycated hemoglobin, CHA2DS2-VASc score, left atrium dimension, and mitral regurgitation did not indicate a differential treatment effect of semaglutide in preventing freedom from atrial arrhythmia recurrence at 12 months in patients undergoing ablation (P value for interaction >0.05; Figure S4).

Sensitivity Analyses

Initial sensitivity analyses were performed by excluding patients lost to follow-up. In model 1, adjusted for age, sex, persistent AF, AF history ≥12 months, BMI, glycated hemoglobin, left atrium dimension, left ventricular ejection fraction, and moderate or more severe mitral regurgitation, treatment with semaglutide was associated with a reduced risk of atrial arrhythmia recurrence during the 12-month follow-up period (model 1; Table S6). Further adjustments for baseline use of antiarrhythmic drugs (amiodarone, propafenone, dronedarone, beta blockers) did not alter these findings (model 2; Table S6). Additional adjustments for baseline use of antidiabetic drugs (SGLT-2 [sodium-glucose cotransporter 2] inhibitors, metformin, DPP-4 [dipeptidyl peptidase 4] inhibitors, insulin, α-glucosidase inhibitors, sulfonylureas,

Table 3. Univariable and Multivariable Cox Proportional Hazard Model

Characteristic	Univariable			Multivariable		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age, y	1.00	(0.98–1.02)	0.765			
Male	0.78	(0.56–1.09)	0.142			
Semaglutide	0.68	(0.48–0.98)	0.036	0.66	(0.46–0.95)	0.025
Persistent AF	1.38	(0.96–1.99)	0.081	1.18	(0.80–1.74)	0.406
AF history ≥12 m	1.36	(0.98–1.88)	0.070	1.40	(1.01–1.96)	0.047
Hypertension	1.45	(0.97–2.17)	0.070	1.52	(1.01–2.28)	0.046
Coronary heart disease	1.23	(0.84–1.80)	0.279			
Stroke	1.44	(0.97–2.14)	0.073	1.44	(0.96–2.18)	0.080
Heart failure	1.54	(0.99–2.41)	0.057	1.16	(0.68–1.98)	0.597
BMI	1.02	(0.95 ≈ 1.09)	0.541			
Obstructive sleep apnea	1.54	(0.94 ≈ 2.53)	0.086	1.52	(0.92–2.52)	0.101
Glycated hemoglobin	1.05	(0.91–1.22)	0.489			
LAD, mm	1.03	(1.00–1.06)	0.073	1.01	(0.97–1.04)	0.687
LVEF	0.98	(0.96–1.00)	0.087	0.99	(0.96–1.02)	0.441
Moderate or more severe mitral regurgitation	1.80	(1.12–2.89)	0.014	1.54	(0.92–2.58)	0.098
SGLT-2 inhibitors	0.94	(0.59–1.50)	0.809			
Metformin	1.13	(0.81–1.57)	0.469			
DPP-4 inhibitors	0.98	(0.63–1.55)	0.944			
Insulin	0.85	(0.53–1.36)	0.485			
α-glucosidase inhibitors	1.07	(0.73–1.57)	0.726			
Sulfonylureas	0.89	(0.53–1.50)	0.664			
Thiazolidinediones	1.00	(0.53–1.90)	0.996			

Variables with $P<0.01$ in univariable screening and prespecified clinically significant covariates were entered into the multivariable Cox proportional hazard model. AF indicates atrial fibrillation; BMI, body mass index; DPP-4, dipeptidyl peptidase 4; HR, hazard ratio; LAD, left atrium dimension; LVEF, left ventricular ejection fraction; and SGLT-2, sodium-glucose cotransporter 2.

thiazolidinediones) similarly did not change the results (model 3; Table S6). Further inclusion of baseline prevalent conditions, such as hypertension, coronary heart disease, stroke, obstructive sleep apnea, and congestive heart failure, also did not affect the outcomes (model 4; Table S6). Comprehensive adjustments for baseline use of ADDs, antidiabetic drugs, and prevalent conditions, including hypertension, coronary heart disease, stroke, and congestive heart failure, remained consistent with the initial findings (model 5; Table S6). Replacement of the end point from freedom from atrial arrhythmias to AF recurrence in the Cox proportional hazard model analysis yielded unchanged results (model 6; Table S6). In model 7, inclusion of patients who reduced or discontinued semaglutide during the follow-up period in the control group in the Cox proportional hazard model analysis did not alter the study findings (model 7; Table S6). Finally, replacement of the end point from freedom from atrial arrhythmias to freedom from atrial arrhythmia recurrence without antiarrhythmic drugs also did not alter the study findings (model 8; Table S6).

Subsequently, to mitigate the impact of loss to follow-up and medication reduction/discontinuation on study outcomes, we performed sensitivity analyses of the primary outcome, incorporating 40 lost-to-follow-up patients through intention-to-treat and per-protocol set analyses. These included best-case scenario, worst-case scenario, and multiple imputation for missing outcomes. After adjusting for sex, age, baseline use of ADDs, and prevalent conditions, the results remained unchanged (Table S7).

Finally, to minimize the influence of medication reduction/discontinuation, we conducted on-treatment sensitivity analyses by excluding patients who reduced or discontinued medications. The results remained consistent after adjusting for covariates similar to those in the aforementioned models (Table S8).

DISCUSSION

This multicenter prospective study evaluated the effects of semaglutide on atrial arrhythmia recurrence, weight loss, and glycemic control in overweight or obese patients with AF and type 2 diabetes following catheter ablation. Our findings demonstrate that the semaglutide group had a higher rate of freedom from atrial arrhythmia recurrence during the 12 months postablation, alongside substantial improvements in weight and glycated hemoglobin levels. To our knowledge, this is the first prospective study to investigate the relationship between semaglutide use postablation and atrial arrhythmia recurrence.

Comparison With Previous Studies

The potential antiarrhythmic effects of GLP-1 RAs have been explored in several studies. A 2021 network meta-analysis suggested that GLP-1 RAs may reduce the risk of AF or atrial flutter in diabetic patients compared with other antidiabetic drugs.[25] Similarly, real-world studies have reported a lower risk of AF in type 2 diabetes patients treated with GLP-1 RAs.[26] Preclinical evidence supports these findings, as GLP-1 receptors are highly expressed in the atria, and GLP-1 has been shown to reduce AF and prevent atrial remodeling in animal models.[27,28] Recent meta-analyses have further confirmed the association between semaglutide and reduced AF risk.[29,30] However, conflicting evidence persists; a meta-analysis published in 2022 concluded that GLP-1RAs had no significant effect on the risk of arrhythmias in type 2 diabetes patients.[31] A real-world study conducted in Spain also found that GLP-1RAs use did not have a significant impact on the risk of AF.[32]

The evidence regarding GLP-1 RAs and AF recurrence postablation remains limited. A large real-world study found no reduction in AF recurrence risk with preablation GLP-1 RA treatment.[33] This neutral effect may stem from the high discontinuation rates of GLP-1RAs due to gastrointestinal side effects and treatment costs, potential heterogeneity in cardiovascular benefits across different GLP-1RAs subtypes, and the study's lack of analysis on weight reduction or glycemic control—key mechanisms through which GLP-1RAs exert therapeutic effects. Conversely, a meta-analysis reported that GLP-1RAs use was associated with reduced AF recurrence risk in patients undergoing ablation.[34] And the recent landmark LEAF randomized trial (n=55, BMI ≥27 kg/m^2) demonstrated that intensive preablation therapy with liraglutide 1.8 mg daily plus risk factor modification, when initiated 3 months preprocedure, yielded superior outcomes versus standard risk factor modification alone. At 3-year follow-up, the risk factor modification plus liraglutide group showed markedly lower AF recurrence rates (29.6% versus 67.5%; $P<0.01$).[35] Importantly, the benefits appeared to extend beyond simple weight loss, suggesting direct modulation of atrial myopathy substrates independent of pulmonary vein triggers. Our findings align with existing evidence, showing that early postablation semaglutide use was associated with a lower rate of atrial arrhythmia recurrence and significant metabolic improvement. This research suggests GLP-1 receptor agonists may represent a potential adjunctive therapy through combined metabolic effects and possible antiarrhythmic mechanisms.

Clinical Implications and Future Directions

Semaglutide and other GLP-1 RAs are emerging dual-action therapies for weight loss and glycemic control. Notably, weight loss achieved with semaglutide combined with exercise appears stable, with no rebound effect after discontinuation.[36–38] However, the impact of semaglutide-induced weight loss on AF recurrence postablation has been underexplored. Our study addresses this gap,

showing that semaglutide significantly reduces atrial arrhythmia recurrence in patients with AF postablation.

Subgroup analysis revealed that semaglutide's benefits were more pronounced in patients with BMI ≥27 kg/m^2, suggesting greater efficacy in individuals with higher BMI. This aligns with previous findings that GLP-1 RAs induce more significant weight loss in higher BMI populations. The differential weight loss effects may explain the enhanced benefit in these patients.

Interestingly, this study revealed a notably high incidence of digestive tract symptoms (43.83%) in the semaglutide group, along with an 11.6% rate of treatment discontinuation due to adverse events or other reasons. Although most patients experienced mild and tolerable gastrointestinal symptoms that did not interrupt ongoing semaglutide therapy, the observed reduction in treatment adherence attributable to these side effects poses a practical challenge for clinical application.

The antiarrhythmic mechanisms of GLP-1 RAs remain incompletely understood. Beyond weight loss and glycemic control, GLP-1 receptors in the atria may modulate atrial function through pathways involving PKA (protein kinase A), CaMKII (calcium/calmodulin-dependent protein kinase II), and NCX (sodium-calcium exchanger), as well as intracellular Ca^{2+} homeostasis.[39] Preclinical studies in db/db mice have shown that GLP-1 prevents AF by mitigating atrial conduction damage, electric remodeling, and fibrosis, suggesting that GLP-1 plays a crucial role in regulating atrial function.[27,28]

Study Limitations

This study has several limitations. First, as a nonrandomized study with self-selected treatment groups, potential selection bias may exist—patients choosing semaglutide might have differed from controls in unmeasured factors (eg, health-seeking behaviors or treatment adherence), and residual confounding may persist despite multivariable adjustments. Second, the open-label design introduces possible placebo effect bias, particularly for subjective outcomes (eg, symptom reporting), as patients and clinicians were aware of treatment assignments. Third, AF recurrence was assessed via patient self-reports and intermittent ECG monitoring, which may underestimate asymptomatic episodes; future studies should adopt continuous monitoring (eg, implantable loop recorders) to improve detection accuracy. Fourth, the BMI inclusion threshold (≥24 kg/m^2) reflects East Asian definitions of overweight/obesity but limits generalizability to Western populations, where higher BMI criteria are standard. Further investigations in broader BMI ranges are needed. Fifth, the 1.0 mg weekly subcutaneous semaglutide dose—selected for glycemic control in Chinese patients with lower baseline weight—precludes evaluation of the 2.4 mg dose (used for weight management elsewhere but unavailable in mainland China), warranting dose-response studies. Sixth, the modest sample size hindered subgroup analyses to identify populations most likely to benefit, and the exclusively Chinese cohort necessitates validation in multiethnic, international trials to ensure broader applicability. Finally, as our study population primarily comprised East Asian individuals, the generalizability of these findings to other ethnic groups remains uncertain. Given known ethnic variations in AF substrate characteristics and drug responses, further validation in diverse populations is warranted.

Conclusions

In patients with type 2 diabetes and BMI ≥24 kg/m^2 undergoing catheter ablation for AF, those treated with semaglutide demonstrated a lower rate of atrial arrhythmia recurrence, along with significant weight loss and improved glycemic control, compared with nonusers. However, these results require further validation through multicenter randomized controlled trials.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

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