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Aggressive Risk Factor Reduction Study for Atrial Fibrillation Implications for Ablation Outcomes
The ARREST-AF Randomized Clinical Trial

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IMPORTANCE Atrial fibrillation (AF) ablation outcomes demonstrate attrition over time. Although observational studies have reported reduced arrhythmia recurrence after AF ablation with aggressive lifestyle and risk factor modification, evidence from randomized clinical trials is lacking.

OBJECTIVE To determine the impact of risk factor and weight management on AF ablation rhythm outcomes.

DESIGN, SETTING, AND PARTICIPANTS This was an open-label, multicenter, randomized clinical trial with 12-month follow-up conducted from July 2014 to September 2018. The setting included 3 sites in Adelaide, South Australia. Included in the analysis were consecutive patients with nonpermanent symptomatic AF undergoing first-time catheter ablation with a body mass index (BMI) greater than or equal to 27 (calculated as weight in kilograms divided by height in meters squared) and 1 or more additional cardiometabolic risk factors. Data were analyzed from September 2023 to August 2024.

INTERVENTIONS Patients were randomized 1:1 to lifestyle and risk factor management (LRFM) or usual care (UC) at catheter ablation. The LRFM group was treated in a structured, physician-led tailored clinic to reduce modifiable risk factors. The UC group was given information on management of risk factors by their treating physician but were not enrolled into the risk factor modification clinic. Both groups received guideline-directed care for management of AF by a team blinded to randomization. Pulmonary vein isolation was undertaken in each patient with additional ablation considered at the discretion of the electrophysiologist.

MAIN OUTCOMES AND MEASURES Proportion of patients free from AF in the 12-month period after ablation.

RESULTS Of 122 participants (mean [SD] age, 60 [10] years; 82 male [67%]; mean [SD] BMI, 33 [5]), 62 were randomized to LRFM, and 60 were randomized to UC. Primary end point at 12 months after ablation was observed in 38 patients (61.3%) in the LRFM group and 24 (40%) in the control group (P = .03). The hazard for recurrent arrhythmia over 12 months was 0.53 (95% CI, 0.32-0.89) for LRFM vs UC. AF symptom severity was significantly improved in the LRFM group compared with the UC group (mean difference, −2.0; 95% CI, −3.7 to −0.3). Patients in the LRFM group achieved a significantly improved risk factor profile compared with those in the UC group (mean difference, body weight, −9.0 kg; 95% CI, −11.1 to −6.8 kg and waist circumference, −7.0 cm; 95% CI, −9.4 to −4.5 cm were lower at 12 months in the LRFM group; systolic BP was lower at 12 months in the LRFM group, −10.8 mm Hg; 95% CI, −16.1 to −5.5 mm Hg, although there was no difference in diastolic BP, −3.5 mm Hg; 95% CI, −7.2 to 0.2 mm Hg).

CONCLUSIONS AND RELEVANCE Among patients with AF, elevated BMI, and 1 or more additional cardiometabolic risk factors, aggressive risk factor management reduced arrhythmia recurrence over the 12-month period after catheter ablation. These findings demonstrate the importance of LRFM for the maintenance of sinus rhythm after catheter ablation.

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Visual Abstract

Supplemental content

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Atrial fibrillation (AF) is the most common clinically significant arrhythmia, growing in prevalence and disease burden.[1,2] The development of AF is driven largely by the presence of modifiable cardiac risk factors including hypertension, diabetes, obesity, and obstructive sleep apnea (OSA).[3] Indeed, with each additional risk factor, the risk of AF increases exponentially.[4-7]

Catheter ablation is an effective therapeutic option in treating AF.[8-10] Catheter ablation as a rhythm control strategy not only significantly reduces AF burden but also substantially improves clinical end points.[11,12] However, with continuous monitoring, over 45% of patients will experience recurrent AF within 12 months,[13] and long-term outcomes of AF ablation demonstrate further attrition with time.[14,15] The presence of modifiable cardiac risk factors is associated with more frequent recurrence of AF.[16-18] Although observational studies demonstrate reduced arrhythmia recurrence after AF ablation in patients who undergo aggressive lifestyle and risk factors modification (LRFM), evidence from randomized clinical trials is lacking.[19-21]

We hypothesize that the aggressive and comprehensive LRFM will improve AF ablation outcomes. This study aims to evaluate the impact of aggressive cardiac risk factor and weight management on arrhythmia recurrence in the 12 months after catheter ablation.

Key Points

Question Among patients with atrial fibrillation undergoing catheter ablation, does lifestyle and risk factor management improve 12-month freedom from arrhythmia recurrence?

Findings In this randomized clinical trial, among 122 patients with symptomatic atrial fibrillation undergoing de novo catheter ablation, lifestyle and risk factor management improved the primary end point of arrhythmia freedom at 12 months after ablation when compared with usual care.

Meaning This finding demonstrates the need for comprehensive risk factor management to reduce arrhythmia recurrence after catheter ablation.

Methods

Trial Design and Oversight

We conducted this investigator-initiated, multicenter, open-label, randomized clinical trial at 3 participating institutions (Royal Adelaide Hospital, Ashford Hospital, and Calvary Adelaide Hospital, in Adelaide, Australia). This study was designed to evaluate the impact of aggressive LRFM on the outcomes of catheter ablation. An overview of the study design and protocol are provided in Supplement 1. The statistical analysis plan is available in Supplement 2. The trial design and conduct were overseen by an academic steering committee. This study was conducted using the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Trial Participants and Randomization

The study comprised consecutive individuals with paroxysmal or persistent AF undergoing de novo catheter ablation for symptomatic drug refractory AF between July 2, 2014, and September 7, 2017, with a 12-month follow-up to September 7, 2018. For inclusion, participants were required to have a body mass index (BMI) greater than or equal to 27 (calculated as weight in kilograms divided by height in meters squared) and 1 or more additional risk factors. Detailed inclusion and exclusion criteria are presented in eTable 1 in Supplement 3.

Eligible patients were randomized in a 1:1 ratio to LRFM or usual care (UC) using a computer-generated randomization schedule with random block sizes of 2 to 6 patients per block. Randomization was performed at the time of ablation and concealed from the electrophysiologist undertaking ablation. All patients provided written informed consent to the study protocol that was approved by the Human Research Ethics Committee of the Central Adelaide Local Health Network and the University of Adelaide, Adelaide, Australia. Participant race and ethnicity data were not included in this study.

Study Protocol

Risk Factor Management Group

Patients in the LRFM group attended a physician-directed LRFM clinic (in addition to arrhythmia follow-up) every 3 months and were treated according to American Heart Association guidelines at the time of study.[22] The aggressive LRFM methodology and targets used have been previously described (eMethods in Supplement 3).[23,24]

Blood Pressure Control Blood pressure (BP) was measured twice daily using a home-based automated sphygmomanometer with an appropriate-sized cuff. Exercise stress testing was performed to determine the presence of exercise-induced hypertension with BP greater than 200/100 mm Hg considered as evidence to optimize therapy. Lifestyle advice constituted dietary salt restriction. Pharmacotherapy was initiated using renin-angiotensin-aldosterone system antagonists with other agents used where necessary to achieve a target BP less than 130/80 mm Hg at least 80% of the time. The patient-maintained BP diary was corroborated via in-office and 24-hour ambulatory BP measurements, as required.

Weight Management A structured motivational and goal-directed program using face-to-face counseling was used for weight reduction as previously outlined.[23,24] The weight-loss clinic was run by a dedicated physician responsible for delivering the risk factor reduction program. The physician responsible for this program was distinct to those responsible for AF treatment. At the commencement of the weight-loss intervention, the patient was educated on the benefits of weight management for AF management. Initial weight reduction was attempted by a meal plan coupled with behavior modification. Meals consisting of high-protein and low-glycemic index, calorie-controlled foods were recommended. A specific focus was applied to reducing between-meal snacking and limiting portion sizes. Each meal plan was individualized to patient preferences. The target weight loss was 10% of initial body mass with an aim of reducing BMI to less than 27. Throughout the course

of the weight-loss intervention, gradual weight reduction was preferred targeting 1% to 2% per month, agreed on between the physician and patient at each review. To supplement the dietary effects on weight management, low-intensity aerobic exercise was initially prescribed for 20 minutes, 3 times per week. The volume and intensity of aerobic exercise was progressively increased, to a target of 210 minutes per week of moderate intensity exercise.[25] Participants were required to maintain a lifestyle journal consisting of daily food intake, BMI, and exercise duration to be considered at each review. The lifestyle journal enabled consideration of dietary behaviors that may prevent target weight loss, while providing an effective behavioral tool for patients to self-reflect and monitor eating habits.

Lipid Management Lipid levels were initially managed with lifestyle measures. If patients were unable to achieve low-density lipoprotein (LDL) cholesterol less than 100.4 mg/dL (to convert to millimoles per liter, multiply by 0.0259) after 3 months then an HMG-CoA reductase inhibitor was initiated. Fibrates were used for isolated hypertriglyceridemia (triglyceride level > 495.6 mg/dL; to convert to millimoles per liter, multiply by 0.0113) or added to statin therapy if triglyceride level was greater than 203.5 mg/dL and non-high-density lipoprotein (HDL) cholesterol level was greater than 131.3 mg/dL (to convert to millimoles per liter, multiply by 0.0259).

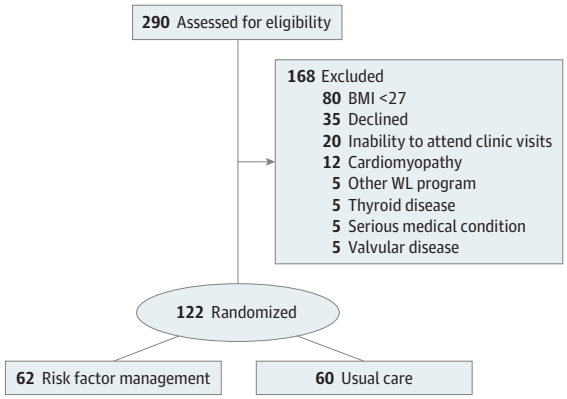
Glycemic Control If fasting glucose was 100.9 to 124.3 mg/dL (to convert to millimoles per liter, multiply by 0.0555), a glucose tolerance test was performed. Impaired glucose tolerance or diabetes was initially managed with lifestyle measures. If patients were unable to maintain glycosylated hemoglobin less than or equal to 6.5% after 3 months, metformin was started. Patients with suboptimal glycemic control (hemoglobin A_{1c} >7%; to convert to proportion of total hemoglobin, multiply by 0.01) were referred to a specialized diabetes clinic.

Sleep-Disordered Breathing Management In-laboratory overnight polysomnography was scored by qualified sleep technicians and reviewed with follow-up by a sleep physician. Polysomnography scoring was according to the American Academy of Sleep Medicine alternate polysomnography scoring criteria.[26] Patients were offered therapy if the Apnea-Hypopnea Index was greater than or equal to 30 or if it was greater than 20 with resistant hypertension or problematic daytime sleepiness. Treatment included positional therapy and continuous positive airway pressure (CPAP).

Smoking The 5A's (ie, ask, advise, assess, assist, and arrange follow-up) structured smoking cessation framework was adopted. Smokers were offered behavioral support through a multidisciplinary clinic with the aim of cessation.

Alcohol Consumption Written and verbal counseling was provided with regular supportive follow-up for alcohol reduction to less than or equal to 30 g/week.

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) Diagram Demonstrating Patient Recruitment and Attrition



Of the 290 patients, 168 were excluded from the analysis as detailed; 122 patients were randomized to lifestyle and risk factor management (62 patients) or control (60 patients) group. BMI indicates body mass index; WL, weight loss.

UC Group

Patients randomized to UC were given information on management of risk but were not enrolled into the LRFM clinic. These patients were given written and verbal advice regarding health nutrition and exercise guidelines at commencement of their participation and weight management is a self-directed process. Completion of a diet and activity diary was not requested. Follow-up was scheduled every 3 months for a 20- to 40-minute physician-led major assessment, as for the intervention group.

Catheter Ablation and AF Management

The ablation procedure was performed with the operator blinded to randomization. The ablation technique used at our institution has been previously described.[27] The ablation strategy included wide-encircling pulmonary vein (PV) ablation with an end point of electrical isolation in all patients. Further substrate modification was performed for patients with AF episodes for 48 hours or longer or if the largest left atrial dimension exceeded 57 mm. This included linear ablation (roofline and/or mitral isthmus) with an end point of bidirectional block and/or electrogram-guided ablation of fractionated sites.

If patients developed recurrent arrhythmia after the blanking period (3 months), repeat ablation was offered. Individual operators decided on the extent of additional ablation undertaken beyond reisolation of the PVs. Details of the ablation procedures are provided in the eMethods in Supplement 3.

Follow-Up

Patients were reviewed for arrhythmia recurrence by physicians blinded to randomization. Patients had an implantable loop recorder (ILR) at the time of randomization, and AF was monitored through home monitoring. Automatic transmissions from the ILR were obtained on a monthly basis. In-clinic reviews were every 3 months. At each review, AF recurrence was ascertained

Table 1. Baseline Characteristics

Baseline characteristic	Usual care (n = 60)	Lifestyle risk factor management (n = 62)
Sex, No. (%)		
Female	21 (35)	19 (31)
Male	39 (65)	43 (69)
Age, mean (SD), y	59 (10)	62 (9)
Risk factor profile		
Body mass index,[a] mean (SD)	33.6 (5.4)	32.8 (5.3)
Persistent AF, No. (%)	34 (56.7)	38 (61.3)
Hypertension, No. (%)	45 (75)	44 (71)
Type 2 diabetes, No. (%)	9 (15.0)	8 (12.9)
Obstructive sleep apnea, No. (%)	27 (45)	22 (35.5)
Stroke/TIA, No. (%)	6 (10.0)	3 (4.8)
History of smoking, No. (%)	22 (36.7)	25 (40.3)
Excess alcohol consumption, No. (%)	21 (35.0)	22 (35.5)
Ischemic heart disease, No. (%)	9 (15.0)	6 (9.7)
Medications		
Aspirin, No. (%)	10 (16.7)	9 (14.5)
Oral anticoagulation, No. (%)	52 (86.7)	52 (83.9)
β-Blocker, No. (%)	28 (46.7)	23 (37.1)
Calcium channel blocker, No. (%)	24 (30.0)	19 (30.6)
Sotalol, No. (%)	11 (18.3)	14 (22.6)
Flecainide, No. (%)	18 (30.0)	17 (27.4)
Amiodarone, No. (%)	7 (11.7)	4 (6.5)
Angiotensin-converting enzyme inhibition, No. (%)	17 (28.3)	18 (29.0)
Angiotensin receptor blockade, No. (%)	23 (38.3)	22 (35.5)
Lipid-lowering therapy, No. (%)	25 (41.7)	21 (33.9)

Abbreviation: TIA, transient ischemic attack.

[a] Calculated as weight in kilograms divided by height in meters squared.

from patients' symptoms, electrocardiography, ambulatory 7-day monitoring, and AF burden/episodes on ILR. These recordings were analyzed by 2 independent observers blinded to patient group. In the absence of any arrhythmia, antiarrhythmic drugs were stopped at 4 to 6 weeks after ablation. All patients were anticoagulated for 3 months or longer after ablation.

AF Symptom Burden

AF symptom burden and severity were quantified using the validated AF Severity Scale (AFSS). The AFSS is a validated scale (range, 3.25 [single minimally symptomatic episode lasting minutes] to 30 [continuous highly symptomatic episode lasting >48 hours]) that encompasses 3 domains of AF: event frequency (scored 1-10), duration (scored 1.25-10), and global episode severity (scored 1-10). In addition, the AFSS assesses symptom severity via an associated symptom-specific continuous subscale (range, 0 [no symptoms] to 35 [severe symptomatology]) as shown in eFigure 3 in Supplement 3.[28] The AFSS questionnaire was administered at baseline and 12-month follow-up after ablation.

Cardiac Structure

Transthoracic echocardiography was performed by an operator blinded to randomization, at baseline, and at 12-month follow-up, with measures performed according to American Society of Echocardiography guidelines.

Trial End Points

The primary end point was freedom from any atrial tachyarrhythmia (AF or tachycardia) lasting 30 seconds or longer between 91 and 365 days after ablation on ILR. Secondary end points included arrhythmia burden (expressed as the percentage of time in AF), cardiometabolic risk factor outcomes, quality of life as assessed by the AFSS, and serious adverse events. All safety end points were independently adjudicated by a clinical end point committee whose members were unaware of the treatment assignments and patient identification.

Statistical Analysis

The primary outcome of recurrent atrial arrhythmia was compared between the randomized groups according to the intention-to-treat principle. The sample size calculation assumed a recurrence of AF among the UC group of 50% over the 12 months after index catheter ablation. To detect an absolute difference between groups of 25 percentage points in the recurrence of AF, a minimum sample size of 60 patients per group was required to provide (α = .05; β = 0.20).

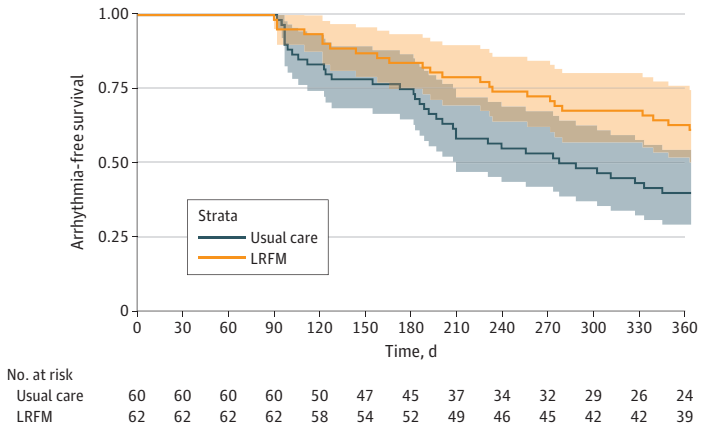
Unadjusted survival curves were estimated using the Kaplan-Meier method. Hazard ratios (HRs) and CIs were assessed from Cox proportional hazards models after checking the proportional hazards assumption. For continuous secondary end points, between-group comparisons were assessed using analysis of covariance with adjustment for baseline values. To account for missing values, a multiple imputation approach was performed using the predictive mean matching method with 50 iterations taken to impute missing values. Fifty imputed datasets were created, which were subsequently pooled for analysis. The CIs of secondary end points are presented without adjustment for multiplicity. Categorical variables are represented by frequencies and percentages. Continuous variables are summarized by mean (SD). All statistical analyses were performed using R statistical software (R Foundation for Statistical Computing) using the mice, rms, survival, and emmeans packages. A 2-sided *P* value <.05 was considered statistically significant. Data were analyzed from September 2023 to August 2024.

Results

Baseline Characteristics

Of 290 consecutive patients referred for de novo catheter ablation of symptomatic AF, 168 were excluded on the basis of predefined exclusions and a further 20 on the basis of inability to attend regular clinic visits (**Figure 1**). The final cohort included 122 patients (mean [SD] age, 60 [10] years; 40 female [33%]; 82 male [67%]; mean [SD] BMI, 33 [5]), of whom 62 were randomly assigned to LRFM and 60 to UC. Patients in both groups were followed up for 12 months from

Figure 2. Arrhythmia-Free Survival Up to 12 Months After Catheter Ablation



No. at risk

Usual care	60	60	60	60	50	47	45	37	34	32	29	26	24
LRFM	62	62	62	62	58	54	52	49	46	45	42	42	39

LRFM indicates lifestyle and risk factor management.

catheter ablation. There were no losses to follow-up. Baseline characteristics are presented in **Table 1** and were well balanced. The details of the catheter ablation procedure are shown in eTable 2 in Supplement 3.

Primary End Point—Arrhythmia-Free Survival

At 12 months after catheter ablation, 38 of 62 patients in the LRFM group (61.3%) vs 24 of 60 patients in the UC group (40.0%) remained free from atrial arrhythmia. Freedom from atrial arrhythmia was statistically greater in the LRFM group compared with the UC group (P = .03). Time-to-event analyses revealed an HR of 0.53 (95% CI, 0.32-0.89) for recurrent atrial arrhythmia over the 12-month follow-up (**Figure 2**), which remained consistent after adjustment for age, type of AF, and biological sex (eTable 3 in Supplement 3).

Secondary End Points

AF Burden and Need for Redo Ablation During the follow-up period, AF burden was low in both groups. For the UC group, median AF burden between 3 and 6, 6 and 9, and 9 and 12 months was 0% (IQR, 0-0.01), 0% (IQR, 0-0.001), and 0% (IQR, 0-0.13), respectively. In the LRFM group, median AF burden was 0% during all 3 periods (eFigure 1 in Supplement 3). Repeat catheter ablation was performed in 10 of 62 patients (16.1%) in the LRFM group, compared with 16 of 60 (26.7%) in the UC group (relative risk, 0.60; 95% CI, 0.30-1.23) (eTable 4 in Supplement 3).

AF Symptoms At 12 months after catheter ablation, patients randomized to LRFM had a lower burden of symptoms compared with those in the control group (**Table 2**). Symptom frequency (mean difference, −2.8 points; 95% CI, −3.8 to −1.9), duration (mean difference, −2.4 points; 95% CI, −3.5 to −1.2), and episode severity (mean difference, −0.8; 95% CI, −1.5 to −0.1) were lower in the LRFM group compared with the UC group. Over the same period, global well-being was greater in the LRFM group (+0.7 points; 95% CI, 0.2-1.3). Total symptom severity was lower in the LRFM group (mean difference, −2.0; 95% CI, −3.7 to −0.3). At 12 months after catheter ablation, 13 of 62 patients (21%) in the LRFM group reported an absence of any AF-related symptoms compared with 3 of 60 patients (5%) in the UC group.

Cardiometabolic Risk Factors

Cardiometabolic risk factors were more favorable in the LRFM group compared with the UC group at 12 months (Table 2 and eFigure 2 in Supplement 3). Body weight (mean difference, −9.0 kg; 95% CI, −11.1 to −6.8 kg) and waist circumference (mean difference, −7.0 cm; 95% CI, −9.4 to −4.5 cm) were lower at 12 months in the LRFM group. Systolic BP was lower at 12 months in the LRFM group (mean difference, −10.8 mm Hg; 95% CI, −16.1 to −5.5 mm Hg), although there was no difference in diastolic BP (mean difference, −3.5 mm Hg; 95% CI, −7.2 to 0.2 mm). Fasting plasma glucose was not different between groups at 12 months (mean difference, −0.2 mmol/L; 95% CI, −0.5 to 0.1 mmol/L). We did not observe any between-group differences in total cholesterol, LDL cholesterol, or HDL cholesterol at 12 months. Exercise capacity was greater in the LRFM group at 12 months compared with the UC group (mean difference, +0.9 metabolic equivalent of task [METs]; 95% CI, 0.3-1.5 METs). Medication usage and additional risk factor control at baseline and 12 months of follow-up are shown in **Table 3**.

Transthoracic Echocardiography

At 12 months, we did not observe any between-group difference in left ventricular systolic or diastolic function. Left atrial volume was comparable between groups at 12 months after catheter ablation. There was no between-group difference in left ventricular chamber dimension or wall thickness (Table 2).

Procedural Complications and Adverse Events

In the LFRM group, 1 patient (1.6%) experienced procedural pericardial effusion, and 1 patient (1.7%) in the UC group developed pericarditis. Pseudoaneurysm was seen in 1 patient in the LRFM group (1.6%), and posterior wall temperature rise limiting catheter ablation was seen in 2 patients (3.4%) in the UC group and 3 patients (5%) in the LRFM group (eTable 5 in Supplement 3). No serious adverse events were seen in either group during follow-up. Two patients (1 LFRM, 1 UC) were hospitalized with rapid AF during follow-up. Six patients (9.7%)

Table 2. Between-Group Differences in Cardiometabolic Risk Factors, Echocardiographic Measures, and Atrial Fibrillation (AF) Symptoms

Measure	Group	Mean (SD)		Mean between-group difference at 12-mo (95% CI)[a]
		Baseline	12 mo	
Cardiometabolic risk factors				
Body weight, kg	LRFM	99.2 (14.5)	90.2 (13.3)	−9.0 (−11.1 to −6.8)
	Usual care	103.0 (19.2)	102.9 (21.8)	
Waist circumference, cm	LRFM	106.6 (10.9)	99.3 (11.2)	−7.0 (−9.4 to −4.5)
	Usual care	109.3 (13.6)	108.9 (15.2)	
Systolic blood pressure, mm Hg	LRFM	137.6 (13.9)	124.5 (15.6)	−10.8 (−16.1 to −5.5)
	Usual care	127.8 (13.9)	131.7 (13.8)	
Diastolic blood pressure, mm Hg	LRFM	81.8 (10.7)	75.9 (9.5)	−3.5 (−7.2 to 0.2)
	Usual care	75.0 (8.1)	78.2 (10.2)	
Fasting plasma glucose, mg/dL	LRFM	99.1 (21.6)	95.5 (16.2)	−3.6 (−9.0 to 1.8)
	Usual care	108.1 (34.2)	104.5 (32.4)	
Total cholesterol, mg/dL	LRFM	177.6 (38.6)	177.6 (38.6)	0 (−11.6 to 11.6)
	Usual care	181.5 (42.5)	177.6 (34.7)	
Low-density lipoprotein, mg/dL	LRFM	100.4 (34.7)	100.4 (30.9)	0 (−7.7 to 11.6)
	Usual care	108.1 (34.7)	100.4 (34.7)	
Triglycerides, mg/dL	LRFM	132.7 (79.6)	115.0 (53.1)	−8.6 (−26.6 to 17.7)
	Usual care	123.9 (53.1)	115.0 (79.6)	
Exercise capacity, METs	LRFM	7.9 (2.4)	8.9 (2.4)	0.9 (0.3 to 1.5)
	Usual care	7.8 (2.3)	8.0 (2.1)	
Transthoracic echocardiography				
Left ventricular ejection fraction, %	LRFM	59.7 (9.2)	61.1 (6.4)	0.4 (−1.9 to 2.8)
	Usual care	59.8 (7.0)	60.7 (7.4)	
Left atrial volume, mL	LRFM	78.8 (23.3)	69.8 (22.5)	−3.7 (−8.2 to 0.8)
	Usual care	79.6 (22.8)	65.6 (11.9)	
Indexed left atrial volume, mL/m^2	LRFM	36.0 (9.7)	31.6 (5.5)	0 (−2.1 to 2.1)
	Usual care	35.7 (9.2)	31.4 (9.7)	
Left ventricular diameter, cm	LRFM	5.1 (0.5)	5.0 (0.5)	0 (−0.2 to 0.1)
	Usual care	5.1 (0.6)	5.0 (0.6)	
Interventricular septal thickness, cm	LRFM	1.0 (0.1)	1.0 (0.2)	0 (−0.1 to 0)
	Usual care	1.1 (0.2)	1.0 (0.2)	
Atrial fibrillation symptoms				
Symptom frequency	LRFM	6.2 (2.7)	1.9 (1.9)	−2.8 (−3.8 to −1.9)
	Usual care	5.5 (3.0)	4.5 (2.8)	
Symptom duration	LRFM	6.9 (2.7)	3.7 (3.1)	−2.4 (−3.5 to −1.2)
	Usual care	5.7 (3.1)	5.6 (3.0)	
Episode severity	LRFM	5.4 (2.3)	4.1 (2.2)	−0.8 (−1.5 to −0.1)
	Usual care	5.1 (2.1)	4.7 (2.1)	
Symptom severity	LRFM	9.7 (7.6)	4.6 (4.8)	−2.0 (−3.7 to −0.3)
	Usual care	10.3 (7.7)	6.8 (5.4)	
Global well-being	LRFM	6.8 (2.0)	8.1 (1.4)	0.7 (0.2 to 1.3)
	Usual care	7.1 (1.8)	7.4 (1.6)	

Abbreviations: LRFM, lifestyle and risk factor management; MET, metabolic equivalent of task.

SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.0555; total cholesterol and low-density lipoprotein cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113.

[a] Comparisons at 12 months between randomization groups are adjusted for baseline values.

in the LFRM group and 12 (19.4%) in the UC group required direct-current cardioversion during follow-up (eTable 4 in Supplement 3).

Discussion

This randomized clinical trial demonstrates that in patients with highly symptomatic drug refractory AF undergoing ablation, a structured physician-directed LRFM program resulted in significant reduction in AF recurrence. These findings underscore the importance of treating underlying risk factors to improve rhythm control strategies.

Catheter ablation is an effective therapeutic option for rhythm control in patients with AF. The past 2 decades have witnessed the introduction of novel AF ablation technology and strategies for both paroxysmal and persistent AF, but procedural success defined by recurrent arrhythmia has not improved commensurately.[13,29-31] Although the majority of early AF recurrences are attributable to PV reconnections, when AF recurs after a postablation period of AF quiescence, PV reconnection is much less prevalent.[32-36] These late recurrences are often due to non-PV mechanisms and indicate the progression of atrial remodeling beyond the PV—a phenomenon strongly associated with the presence of cardiometabolic risk factors.[18,37-39]

Table 3. Medication and Risk Factor Control Within Each Group at Baseline and 12-Month Follow-Up

Medication/risk factor	Time point	Usual care (n = 60)	Risk factor management (n = 62)
Medication			
Aspirin, No. (%)	Baseline	10 (16.7)	9 (14.5)
	12 mo	4 (6.7)	6 (9.7)
Oral anticoagulation, No. (%)	Baseline	52 (86.7)	52 (83.9)
	12 mo	41 (68.3)	43 (69.4)
β-Blocker, No. (%)	Baseline	28 (46.7)	23 (37.1)
	12 mo	21 (35)	19 (30.6)
Calcium channel blocker, No. (%)	Baseline	24 (30.0)	19 (30.6)
	12 mo	29 (48.3)	18 (29.0)
Sotalol, No. (%)	Baseline	11 (18.3)	14 (22.6)
	12 mo	4 (6.7)	6 (9.7)
Flecainide, No. (%)	Baseline	18 (30.0)	17 (27.4)
	12 mo	6 (10)	5 (8.1)
Amiodarone, No. (%)	Baseline	7 (11.7)	4 (6.5)
	12 mo	1 (1.7)	0 (0)
Angiotensin-converting enzyme inhibition, No. (%)	Baseline	17 (28.3)	18 (29.0)
	12 mo	14 (23.4)	16 (25.8)
Angiotensin receptor blockade, No. (%)	Baseline	23 (38.3)	22 (35.5)
	12 mo	28 (46.7)	21 (33.9)
Lipid-lowering therapy, No. (%)	Baseline	25 (41.7)	21 (33.9)
	12 mo	30 (50)	23 (37.1)
Risk factor control			
Continuous positive airway pressure, No. (%)	Baseline	6 (10)	5 (8.1)
	12 mo	7 (11.7)	14 (22.6)
Excess alcohol consumption >30 g/wk, No. (%)	Baseline	21 (35)	22 (35.5)
	12 mo	17 (28.3)	3 (4.8)
Current smoking, No. (%)	Baseline	4 (6.7)	3 (4.8)
	12 mo	3 (5)	1 (1.6)

The presence of modifiable risk factors is associated with a more advanced atrial substrate,[40,41] potentially driving the greater recurrence of AF in patients with a higher burden of risk factors at the time of ablation. It seems probable that unrecognized or undertreated risk factors promote progression of atrial remodeling in patients with initially successful AF ablation resulting in eventual recurrence. Indeed, the presence of a progressive arrhythmogenic atrial substrate has been demonstrated even after successful catheter ablation of AF.[36]

There is accumulating evidence to suggest that treatment of underlying risk factors reduces AF burden and recurrence of atrial arrhythmias after ablation. In a randomized clinical trial,[42] weight loss and cardiometabolic risk factor reduction reduced AF symptoms and arrhythmia burden. Observational trials have demonstrated the graded benefit in AF recurrence and progression with increasing weight loss.[19,43] Similarly, emerging data has indicated that CPAP for OSA is associated with reversal of atrial remodeling[44] and improved ablation outcomes.[18] Randomized clinical trials of alcohol abstinence[45] and aerobic exercise intervention[46] demonstrate a reduction in AF episodes and symptoms in the absence of catheter ablation. In patients with uncontrolled hypertension, the addition of renal denervation to catheter ablation reduced AF burden over 3-year follow-up.[47] The current study extends this evidence by demonstrating that LRFM initiated in patients undergoing catheter ablation promotes sinus rhythm maintenance after catheter ablation.

The role of LRFM in the context of rhythm control requires careful consideration. In a prior randomized clinical trial,[48] weight loss alone did not improve AF burden in the 12 months after ablation. However, the magnitude of weight loss achieved was modest (approximately 4.5%). More recently, LRFM and antiarrhythmic therapy has been compared against catheter ablation alone in the PRAGUE-25 trial.[49] Over a 12-month follow-up, AF recurrence was significantly lower in the catheter ablation arm, although there was no evidence for a difference in AF burden and AF symptoms. The data presented here provide evidence for the additive benefit of LRFM to ablation for the reduction of recurrent AF.

Our intervention was tailored to treat multiple risk factors predisposing to AF recurrence. Studies that have focused on a single risk factor in isolation have been less successful at improving ablation outcomes. In the Substrate Modification With Aggressive Blood Pressure Control (SMAC-AF) study, aggressive management of modest hyper-

tension did not change ablation outcomes.[50] Similarly, isolated weight loss without additional risk factor reduction did not improve ablation outcomes.[48] These findings are perhaps not surprising when one considers that AF is a manifestation of several, often coexisting risk factors, highlighting the need for a comprehensive approach that targets each relevant risk factor in the given individual.

Reducing the burden of obesity through weight loss is challenging in clinical practice. Our intervention incorporates structured education, shared decision-making regarding meal planning and behavioral change, and careful follow-up led by a physician in a specialized risk factor clinic. The magnitude of weight loss achieved exceeds that in prior randomized clinical trials (4.5%-5.8%[48,49]) but below that achieved in preceding observational studies (13%[20]) and contemporary pharmacological intervention such as glucagonlike peptide 1 receptor agonists (13%-14%[51,52]).

The current randomized clinical trial in patients undergoing AF ablation demonstrates that structured comprehensive LRFM resulted in improved sinus rhythm maintenance assessed by continuous monitoring. The freedom from AF on continuous monitoring in the LFRM group (61.3%) compares favorably with other studies monitoring AF recurrence by implantable devices, despite the overrepresentation of patients with persistent AF. In a multicenter comparison of patients undergoing cryoballoon vs radiofrequency ablation,[13] 12-month arrhythmia freedom was achieved in 53.9% of patients undergoing radiofrequency catheter ablation for paroxysmal AF. In a comparison of first-line cryoballoon ablation vs drug therapy,[53] AF freedom at 12 months was achieved in 57.1% of patients undergoing first-line cryoballoon ablation. Our study demonstrates that treating underlying risk factors may provide the largest improvement in ablation outcomes above those achieved with advances in technology or ablation strategy alone.

Limitations

This study has some limitations. This was a multicenter Australian study, and we have not evaluated the feasibility of the intervention in other geographies, health care systems, or in culturally and racially diverse populations. Our methodology was to broadly target all components in LRFM, and therefore, we cannot provide insight into the relative contribution of each risk factor or variable treatment targets. Our study was powered to detect a difference in the primary end point of arrhythmia freedom at 12 months postablation. Larger studies are required to determine the potential benefit of LFRM on additional end points such as cardiovascular events. Additionally, catheter ablation within our study was exclusively performed with radiofrequency energy; whether these findings may differ with pulsed field ablation may require further study.

Conclusions

In this randomized clinical trial of patients undergoing catheter ablation with elevated BMI and at least 1 additional lifestyle risk factor, a program of comprehensive LRFM resulted in significant improvement in 12-month AF freedom. This was associated with significant improvements in self-reported AF severity. These findings emphasize that beyond the catheter-based intervention, addressing the LRF drivers of progressive remodeling is critical to achieving the highest rate of long-term sinus rhythm maintenance.

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