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Aggressive Risk Factor Reduction Study for Atrial Fibrillation and Implications for the Outcome of Ablation

The ARREST-AF Cohort Study

Rajeev K. Pathak, MBBS,* Melissa E. Middeldorp,* Dennis H. Lau, MBBS, PhD,* Abhinav B. Mehta, MActSt,† Rajiv Mahajan, MD,* Darragh Twomey, MBBS,* Muayad Alasady, MBBS,*† Lorraine Hanley, BSc,* Nicholas A. Antic, MBBS, PhD,‡ R. Doug McEvoy, MBBS, MD,‡ Jonathan M. Kalman, MBBS, PhD,§ Walter P. Abhayaratna, MBBS, PhD,‖ Prashanthan Sanders, MBBS, PhD*

ABSTRACT

BACKGROUND The long-term outcome of atrial fibrillation (AF) ablation demonstrates attrition. This outcome may be due to failure to attenuate the progressive substrate promoted by cardiovascular risk factors.

OBJECTIVES The goal of this study was to evaluate the impact of risk factor and weight management on AF ablation outcomes.

METHODS Of 281 consecutive patients undergoing AF ablation, 149 with a body mass index ≥27 kg/m^2 and ≥1 cardiac risk factor were offered risk factor management (RFM) according to American Heart Association/American College of Cardiology guidelines. After AF ablation, all 61 patients who opted for RFM and 88 control subjects were assessed every 3 to 6 months by clinic review and 7-day Holter monitoring. Changes in the Atrial Fibrillation Severity Scale scores were determined.

RESULTS There were no differences in baseline characteristics, number of procedures, or follow-up duration between the groups (p = NS). RFM resulted in greater reductions in weight ($p = 0.002$) and blood pressure ($p = 0.006$), and better glycemic control ($p = 0.001$) and lipid profiles ($p = 0.01$). At follow-up, AF frequency, duration, symptoms, and symptom severity decreased more in the RFM group compared with the control group (all $p < 0.001$). Single-procedure drug-unassisted arrhythmia-free survival was greater in RFM patients compared with control subjects ($p < 0.001$). Multiple-procedure arrhythmia-free survival was markedly better in RFM patients compared with control subjects ($p < 0.001$), with 16% and 42.4%, respectively, using antiarrhythmic drugs ($p = 0.004$). On multivariate analysis, type of AF ($p < 0.001$) and RFM (hazard ratio 4.8 [95% confidence interval: 2.04 to 11.4]; $p < 0.001$) were independent predictors of arrhythmia-free survival.

CONCLUSIONS Aggressive RFM improved the long-term success of AF ablation. This study underscores the importance of therapy directed at the primary promoters of the AF substrate to facilitate rhythm control strategies. (J Am Coll Cardiol 2014;64:2222–31) © 2014 by the American College of Cardiology Foundation.

From the *Centre for Heart Rhythm Disorders, South Australian Health and Medical Research Institute, University of Adelaide and Royal Adelaide Hospital, Adelaide, Australia; †Research School of Finance, Actuarial Studies and Applied Statistics, Australian National University, Canberra, Australia; ‡Adelaide Institute for Sleep Health, Repatriation General Hospital and Department of Medicine, Flinders University, Adelaide, Australia; §Department of Cardiology, Royal Melbourne Hospital and the Department of Medicine, University of Melbourne, Melbourne, Australia; and the ‖College of Medicine, Biology and Environment, Australian National University and Canberra Hospital, Canberra, Australia. Dr. Antic has received lecture fees from ResMed and Glaxo-SmithKline; and research grants from Philips Respironics, ResMed, Fisher & Paykel, Compumedics, and SomnoMed. Dr. McEvoy has received lecture fees from Philips Respironics; and research funding from Philips Respironics and ResMed. Dr. Kalman has received lecture fees from Bard Electrophysiology and Biotronik; research support from Medtronic, St. Jude Medical, and Biosense Webster; and travel support from Medtronic and St. Jude Medical. Dr. Sanders has served on the advisory board of Biosense Webster, Medtronic, St. Jude Medical, Sanofi, and Merck Sharp & Dohme; has received lecture fees from Biosense Webster, Medtronic, St. Jude Medical, Boston Scientific, Merck Sharp & Dohme, Biotronik, and Sanofi; and has received research

Atrial fibrillation (AF) affects ~2.7 million people in the United States alone, and its prevalence is expected to rise to 15.9 million by 2050, with a significant impact on health care (1–3). Although population aging is regarded as an important contributor, several risk factors such as hypertension, diabetes mellitus (DM), obesity, and obstructive sleep apnea (OSA) have been linked as promoters of AF (4–7).

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Catheter ablation of AF has evolved as an effective therapy for drug-refractory symptomatic AF (8). Studies have demonstrated the advantage of catheter ablation over pharmacological methods of rhythm control (9–12). However, reports of long-term outcomes of AF ablation demonstrate attrition in success with time (13–17). Studies have associated some cardiac risk factors with more frequent recurrence of AF (18–20). We hypothesized that the attrition in the success of AF ablation is due to progression of the disease process that promoted the development of AF. The goal of the present study was to evaluate the impact of aggressive cardiac risk factors and weight management on outcomes of catheter ablation.

METHODS

STUDY POPULATION. The study comprised consecutive patients with a body mass index (BMI) ≥27 kg/m^2 and ≥1 risk factor (hypertension, glucose intolerance/DM, hyperlipidemia, OSA, smoking, or alcohol excess) undergoing initial catheter ablation for symptomatic AF despite the use of antiarrhythmic medication.

All patients provided written informed consent for the ablation procedure and collection of their clinical data. The Human Research Ethics Committee of the Royal Adelaide Hospital and University of Adelaide approved the study protocol.

STUDY PROTOCOL. All suitable patients were offered risk factor management (RFM) in a dedicated physician-directed clinic at the time of initial assessment. Patients who accepted this strategy formed the intervention group (RFM group), and those who declined formed the control group. Only patients with ongoing significant symptoms, despite the use of antiarrhythmic medications and RFM, underwent AF ablation. Exclusion criteria were: history of myocardial infarction or cardiac surgery in the previous 12 months; previous AF ablation; active malignancy; autoimmune or systemic inflammatory disease; severe renal or hepatic failure; and <12 months' follow-up after their procedure.

RFM GROUP. Patients participating in RFM attended a physician-directed RFM clinic (in addition to their arrhythmia follow-up) every 3 months and were managed according to American College of Cardiology/American Heart Association guidelines (21).

Blood pressure control. Blood pressure (BP) was measured thrice daily by using a home-based automated monitor and an appropriate-sized cuff. In addition, exercise stress testing was performed to determine the presence of exercise-induced hypertension, with BP >200/100 mm Hg considered as evidence to optimize therapy. Lifestyle advice constituted dietary salt restriction. Pharmacotherapy was initiated by using renin-angiotensin-aldosterone system antagonists, with other agents used when necessary to achieve a target BP of <130/80 mm Hg at least 80% of the time. These were corroborated by in-office and 24-h ambulatory BP measurements, as required. Echocardiography was monitored to ensure resolution of left ventricular (LV) hypertrophy.

Weight management. A structured motivational and goal-directed program using face-to-face counseling was used for weight reduction. Patients were encouraged to utilize support counseling and schedule more frequent reviews, as required. Initial weight reduction was attempted by using a meal

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
AFSS = Atrial Fibrillation Severity Scale
AHI = apnea–hypopnea index
BMI = body mass index
BP = blood pressure
CI = confidence interval
CPAP = continuous positive airway pressure
DM = diabetes mellitus
HR = hazard ratio
LA = left atrial
LV = left ventricular
OSA = obstructive sleep apnea

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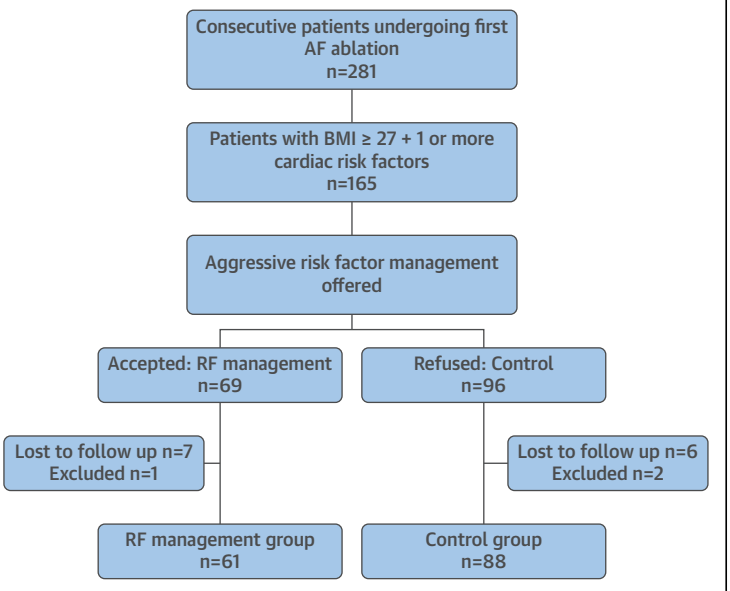


FIGURE 1 Patient Selection

Flow diagram of patient recruitment and attrition. Of 165 patients (69 in the risk factor [RF] management group and 96 in the control group), 16 were excluded from the analysis due to lack of regular follow-up in 13 from other states (7 RF management and 6 control) or systemic illness in 3 (1 with malignancy and 2 with systemic inflammatory diseases). AF = atrial fibrillation; BMI = body mass index.

plan and behavior modification. Participants were required to maintain a diet and physical activity diary. Meals consisted of high-protein and low glycemic index, calorie-controlled foods. If patients lost <3% of weight after 3 months, they were then prescribed very low calorie meal replacement sachets (Prima Health Solutions, Sydney, Australia, or Nestlé Health Science, Sydney, Australia) for 1 to 2 meals per day. The initial goal was to reduce body weight by 10%. After patients achieved the initial goal, meal replacement was substituted with high-protein and low glycemic index, calorie-controlled foods to achieve a target BMI of ≤25 kg/m^2. Low-intensity exercise was prescribed initially for 20 min thrice weekly, increasing to at least 200 min of moderate-intensity activity per week.

Lipid management. Lipids were initially managed with lifestyle measures; if patients were unable to achieve low-density lipoprotein cholesterol levels <100 mg/dl after 3 months, use of a hydroxymethylglutaryl coenzyme A reductase inhibitor was then initiated. Fibrates were used for isolated hypertriglyceridemia (triglycerides >500 mg/dl) or added to statin therapy if triglyceride levels were >200 mg/dl and non-high-density lipoprotein cholesterol levels were >130 mg/dl.

Glycemic control. A glucose tolerance test was performed if fasting glucose levels were 100 to 125 mg/dl. Impaired glucose tolerance or DM was initially managed with lifestyle measures. If patients were unable to maintain glycosylated hemoglobin (HbA_{1c}) levels ≤6.5% after 3 months, metformin was started. Patients in both groups with suboptimal glycemic control (HbA_{1c} >7%) 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. The scoring was according to the American Academy of Sleep Medicine alternate polysomnography scoring criteria (22). Patients were offered therapy if the apnea-hypopnea index (AHI) was ≥30/h or if it was >20/h with resistant hypertension or problematic daytime sleepiness. Treatment included positional therapy and continuous positive airway pressure (CPAP).

Smoking and alcohol. The "5As" (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 smoking cessation.

Written and verbal counseling was provided with regular supportive follow-up for alcohol reduction to ≤30 g/week.

CONTROL GROUP. The control group was given information on management of risk factors. However, they continued RFM under the direction of their treating physician.

CATHETER ABLATION. The ablation procedure was performed with the operator blinded to the patient's study group. The ablation technique used at our institution has been described previously (23) and included wide-encircling pulmonary vein ablation with an endpoint of electrical isolation (pulmonary vein isolation) in all patients. Further substrate modification was performed for patients with AF episodes ≥48 h or if the largest left atrial (LA) dimension exceeded 57 mm. This included linear ablation (roofline and/or mitral isthmus) with an endpoint 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 pulmonary veins.

FOLLOW-UP. Physicians blinded to the patient's study group assessed patients for arrhythmia recurrence. Reviews were every 3 months for the first year

and then every 6 months thereafter. At each review, AF recurrence was ascertained from patients' symptoms, electrocardiograms, and ambulatory 7-day monitoring. Two independent observers blinded to patient group analyzed the ambulatory recordings. In the absence of any arrhythmia, antiarrhythmic drugs were stopped at 4 to 6 weeks. No patient continued on amiodarone after ablation. All patients underwent anticoagulation by using warfarin for ≥3 months after ablation.

Procedural success was determined as the absence of any atrial arrhythmia ≥30 s after a 3-month blanking period.

AF SYMPTOM BURDEN. AF symptom burden and severity were quantified by using the validated Atrial Fibrillation Severity Scale (AFSS, University of Toronto, Toronto, Ontario, Canada) (24). The AFSS is used to quantify 3 domains of AF-related symptoms: frequency, duration, and severity. A symptom subscale was also determined. The AFSS questionnaire was administered at baseline and at follow-up after ablation.

CARDIAC STRUCTURE. Transthoracic echocardiography was performed at baseline and yearly by using a 3.5-MHz probe. Measurements were performed according to American Society of Echocardiography guidelines by an operator blinded to the study group.

STATISTICAL ANALYSIS. Categorical variables are represented by frequencies and percentages, and continuous variables are summarized by mean ± SD. Repeated measure analysis of variance was used to assess the interaction between the groups over time. The significance of the interaction in the analysis of variance was used to assess these changes. Comparisons of variables for both the control and RFM groups were performed by using paired samples Student *t* tests. For nominal variables, such as diabetes and sleep apnea (AHI >30), changes were only assessed for patients who were positive at baseline. The change in the status at final follow-up was compared between the 2 groups by using chi-square tests. The Kaplan-Meier product-limit method was used to estimate the time to recurrence and event-free survival curves after the last ablation procedure. Requirement for a repeat procedure was considered an endpoint. Predictors of recurrent AF were assessed in Cox regression models after verifying proportionality assumptions. Candidate variables with $p < 0.1$ in univariate analyses were considered in multivariate stepwise regression models. Two-tailed p values <0.05 were considered statistically significant. Statistical analysis was performed by using SPSS version 21.0 (IBM SPSS Statistics, IBM Corporation, Armonk, New York).

TABLE 1 Baseline Characteristics

	Control Group (n = 88)	RFM Group (n = 61)	p Value
Age, yrs	57.2 ± 9.9	58.4 ± 10.8	0.5
Male	61 (69.3)	34 (56)	0.1
Anthropometric measures			
Weight, kg	96.6 ± 16.8	100.7 ± 17.6	0.2
BMI, kg/m^2	32.1 ± 4.7	33.5 ± 4.6	0.1
AF type			
Paroxysmal	49 (56)	40 (65)	0.2
Nonparoxysmal	39 (44)	21 (35)	
Metabolic risk factors			
Hypertension	73 (83)	53 (87)	0.5
Diabetes mellitus	17 (19)	9 (15)	0.5
Hyperlipidemia	47 (53)	39 (64)	0.2
Coronary artery disease	10 (11)	10 (16)	0.4
AHI >30	55 (62)	32 (53)	0.2
Alcohol excess (>30 g/week)	24 (27)	11 (18)	0.2
Smoker	31 (35)	20 (33)	0.8
Medication use			
No. of antiarrhythmic agents	1.0 ± 0.2	1.1 ± 0.3	0.1
No. of antihypertensive agents	1.6 ± 1.2	1.5 ± 1.1	0.4
Echocardiographic measures			
LA volume index, ml/m^2	42.4 ± 10.4	42.5 ± 12	0.9
LV septum, mm	11.0 ± 2	12.0 ± 2	0.1
LVIDd, cm	5.1 ± 0.7	5.3 ± 0.5	0.2
LVEF, %	60 ± 10.1	61.1 ± 8	0.5
Atrial Fibrillation Severity Scale			
Frequency (1–10)	6.6 ± 1.1	6.8 ± 1.2	0.5
Duration (1–10)	6.7 ± 1.3	6.4 ± 1.6	0.3
Severity (1–10)	6.9 ± 1.3	6.6 ± 1.5	0.2
Symptom (0–35)	23.1 ± 3.7	22 ± 5.2	0.1
Global well-being (1–10)	2.5 ± 0.9	2.4 ± 0.9	0.4

Values are mean ± SD or n (%).

AF = atrial fibrillation; AHI = apnea-hypopnea index; BMI = body mass index; LA = left atrial; LV = ventricular; LVEF = left ventricular ejection fraction; LVIDd= left ventricular internal dimension in diastole; RFM = risk factor management.

RESULTS

BASELINE CHARACTERISTICS. Of 281 consecutive patients referred for catheter ablation of symptomatic AF, 165 had both BMI ≥27 kg/m^2 and ≥1 risk factor. Of these, 3 patients were excluded on the basis of predefined exclusions (1 with terminal cancer and 2 with systemic inflammatory conditions) and an additional 13 on the basis of the lack of regular follow-up (from other states). The final cohort included 149 patients: 61 RFM patients and 88 control subjects (Figure 1). Mean follow-up in the RFM and control groups were 41.6 ± 12.5 months and 42.1 ± 14.2 months, respectively ($p = 0.8$). Mean duration before the procedure was 9.8 ± 7.1 months in the RFM group and

TABLE 2 Risk Factor, Echocardiographic, and AF Severity Changes

	Control Group (n = 88)			RFM Group (n = 61)			
	Baseline	Follow-Up‡	p Value*	Baseline	Follow-Up‡	p Value*	p Value†
Risk factors							
Weight, kg	96.6 ± 16.8	95.8 ± 17.6	0.13	100.7 ± 17.6	87.5 ± 14.9	<0.001	0.002
BMI, kg/m^2	32.1 ± 4.7	31.8 ± 4.9	0.12	33.5 ± 4.6	29.1 ± 3.9	<0.001	<0.0011
Mean SBP, mm Hg	158.7 ± 21.3	138.2 ± 18.0	<0.001	160.8 ± 20.3	126.8 ± 12.8	<0.001	0.006
DM with HbA_{1c} ≥7%, n	17	5		9	0		0.001
No. with AHI >30	54	46		32	16		<0.001
Medication use							
No. of antiarrhythmic agents	1.0 ± 0.2	0.7 ± 0.7	<0.001	1.1 ± 0.3	0.3 ± 0.6	<0.001	<0.001
No. of antihypertensive agents	1.6 ± 1.2	1.9 ± 1.3	0.2	1.5 ± 1.1	1.2 ± 0.9	0.04	<0.001
Echocardiographic measures							
LA volume index, ml/m^2	42.4 ± 10.4	39.5 ± 12.1	0.07	42.5 ± 12	30.4 ± 8.3	<0.001	0.001
LV septum, mm	11.0 ± 2.0	10.9 ± 0.19	0.047	12.0 ± 2.0	9.6 ± 0.17	<0.001	<0.001
LVIDd, cm	5.1 ± 0.7	5.1 ± 0.6	0.204	5.3 ± 0.5	4.9 ± 0.6	<0.001	0.047
LVEF, %	60 ± 10.1	61.1 ± 8	0.538	61.3 ± 10	62.6 ± 5.5	0.524	0.971
Atrial Fibrillation Severity Score							
AF frequency (1–10)	6.6 ± 1.1	3.2 ± 1.1	<0.001	6.8 ± 1.2	2.0 ± 0.9	<0.001	<0.001
AF duration (1.25–10)	6.7 ± 1.3	3.3 ± 1.3	<0.001	6.4 ± 1.6	2.1 ± 0.9	<0.001	0.001
AF episode severity (1–10)	6.9 ± 1.3	5.2 ± 1.9	<0.001	6.6 ± 1.5	3.3 ± 1.5	<0.001	<0.001
AF symptom subscale (0–35)	23.1 ± 3.7	13.3 ± 6.2	<0.001	22 ± 5.2	7.1 ± 4.6	<0.001	<0.001
Global well-being (1–10)	2.5 ± 0.9	5.7 ± 2.0	<0.001	2.4 ± 0.9	7.6 ± 1.7	<0.001	<0.001

Values are mean ± SD or n. *The p value is for within-group differences (baseline to follow-up). †The p value is for between-group differences over time (group-time interaction). ‡Median follow-up: 42.8 months for the RFM group and 42.4 months for the control group.

DM = diabetes mellitus; HbA_{1c} = glycosylated hemoglobin; SBP = systolic blood pressure; other abbreviations as in Table 1.

10.2 ± 9.2 months in the control group (p = 0.8). Baseline characteristics were similar in the 2 groups (Table 1).

RISK FACTOR MODIFICATION. Table 2 shows the impact of RFM on various cardiac risk factors.

For BP control, there was a greater decline in systolic BP in RFM patients compared with control subjects (34.1 ± 7.5 mm Hg vs. 20.6 ± 3.2 mm Hg; p = 0.003). The number of antihypertensive agents used for BP control decreased with RFM (1.5 ± 1.1 to 1.2 ± 0.9; p = 0.04) and increased in the control group (1.6 ± 1.2 to 1.9 ± 1.3; p = 0.2).

Weight and BMI decreased in both groups but significantly more in the RFM group compared with the control group (-13.2 ± 5.4 kg vs. -1.5 ± 5.1 kg; p = 0.002) (Table 2).

At baseline, 64% of RFM patients and 53% of control subjects had dyslipidemia (p = 0.2). With diet and lifestyle modification, low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol levels were well controlled in 46.2% of RFM patients and 17% of control subjects (p = 0.01). Drug therapy was required in 43.6% of the RFM group and 68.1% of the control group (p = 0.01). At final follow-up, 10.2% (n = 4) of RFM patients and 15% (n = 7) of control subjects still had dyslipidemia.

At baseline, 15% of RFM patients and 19% of control subjects had a history of DM (p = 0.5). An additional 13% of RFM patients and 10% of control subjects were found to have impaired glucose tolerance. At the final follow-up, DM patients in the RFM group had significantly better glycemic control compared with control subjects: HbA_{1c} levels <7% in 100% versus 29%, respectively (p = 0.001).

TABLE 3 Procedure Details

	Control Group	RFM Group	p Value
First procedure	88	61	
PV isolation	88 (100)	61 (100)	0.2
Line ablation	60 (68)	40 (66)	0.7
CAFE	23 (27.1)	21 (34)	0.3
Second procedure	46	28	
PV consolidative ablation	46 (52)	28 (46)	0.08
Line ablation	36 (41)	21 (34)	0.3
CAFE	15 (17)	6 (10)	0.4
Third procedure	13	6	
PV consolidative ablation	13 (28)	6 (21)	0.6
Line ablation	6 (6.8)	5 (8.2)	0.5
CAFE	0	1	0.8

Values are n or n (%).

CAFE = complex atrial fractionated electrograms; PV = pulmonary vein; RFM = risk factor management.

At baseline, 52% of RFM patients and 61% of control subjects had severe OSA (AHI ≥30; p = 0.2). Of these, 16 (50%) RFM patients had an AHI <15, which we regarded as mild or no OSA when retested at follow-up, compared with 8 (15%) control subjects (p < 0.001). Of patients requiring CPAP, compliance with CPAP use was significantly higher in RFM patients compared with control subjects (77% vs. 32%; p = 0.001).

Most patients successfully stopped smoking: 19 (95%) RFM patients and 28 (90.3%) control subjects (p = 0.5). In the RFM group, 9 (81.8%) patients successfully managed to reduce alcohol consumption to <30 g/week, whereas 15 (62.5%) control subjects achieved this goal (p = 0.2).

ABLATION. Groups underwent ablation procedures at similar rates (RFM 1.6 ± 0.7 per patient; control

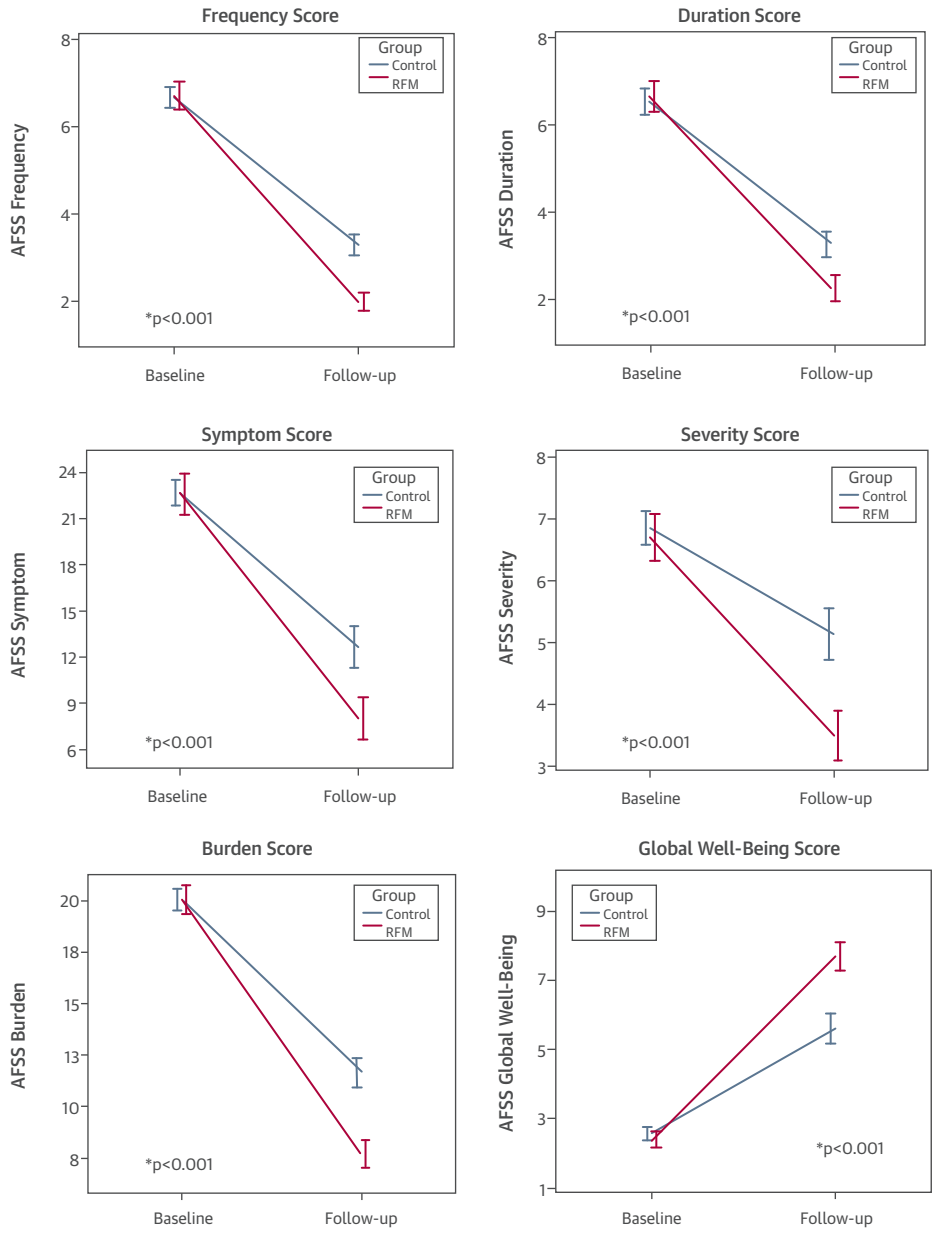


FIGURE 2 Burden of AF

Changes in AF burden according to scores on the Atrial Fibrillation Severity Scale (AFSS) questionnaire at baseline and at final follow-up. **Error bars** indicate 95% confidence intervals. RFM = risk factor management; other abbreviation as in Figure 1.

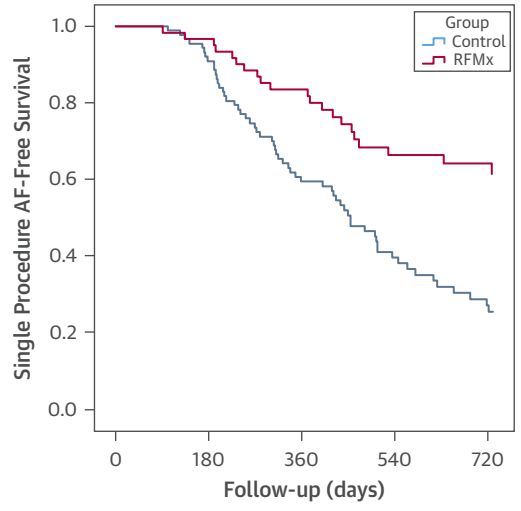
1.5 ± 0.7 [p = 0.3]). Table 3 provides procedural details for each group.

CARDIAC STRUCTURE. Table 2 shows the effect of RFM on cardiac structure. LA volume indexed for body surface area decreased with RFM from 42.5 ± 12.0 ml/m² to 30.4 ± 8.3 ml/m² (p < 0.001) and in control subjects from 42.4 ± 10.4 ml/m² to 39.5 ± 12.1 ml/m² (p = 0.07); this reduction was significantly greater with RFM patients compared with control subjects (p = 0.001). Interventricular septum thickness decreased with RFM from 11.6 ± 1.7 mm to 9.6 ± 1.7 mm (p < 0.001) and in control subjects from 11.3 ± 1.6 mm to 10.9 ± 1.9 mm (p = 0.04). There was a greater reduction in the RFM patients compared with the control subjects (p < 0.001).

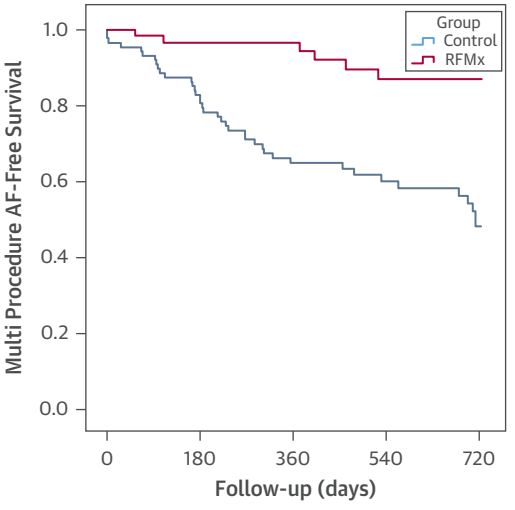
ATRIAL FIBRILLATION. Symptom burden. At baseline, both groups had comparable and high AFSS subscale scores (Table 2). Figure 2 shows changes from baseline to final follow-up for the AFSS subscale pertaining to total AF burden and symptom severity. AF frequency, duration, symptoms, and symptom severity were less at final follow-up in both groups, with a significantly greater reduction seen with the RFM group (p < 0.001). The global well-being score improved by >2-fold after ablation, with the RFM group improving from 2.4 ± 0.9 to 7.6 ± 1.7 (p < 0.001) and the control group improving from 2.5 ± 0.9 to 5.7 ± 2.0 (p < 0.001). However, improvement was markedly better with RFM patients than with control subjects (p < 0.001).

Single-procedure arrhythmia-free survival. Figure 3 demonstrates single-procedure outcomes. At final follow-up, 32.9% of RFM patients versus 9.7% of control subjects (p < 0.001) remained free from arrhythmia. After a single procedure, univariate predictors of AF recurrence were control group (hazard ratio [HR]: 2.6 [95% confidence interval (CI): 1.7 to 4.0]; p < 0.001) and type of AF (nonparoxysmal AF: HR: 1.8 [95% CI: 1.2 to 2.7]; p = 0.004). Both factors remained independent predictors of recurrent AF in multivariate analyses: control group, HR: 2.3 (95% CI: 1.5 to 3.6; p < 0.001) and nonparoxysmal AF, HR: 1.7 (95% CI: 1.1 to 2.5; p = 0.01). Differences in outcomes on the basis of AF type are shown in Online Figure 1.

Multiple interventions arrhythmia-free survival. Figure 3 demonstrates arrhythmia-free survival after multiple procedures, with significant attrition in control subjects compared with RFM patients. At final



Time (days)	0	180	360	540	730
RFM	61	59	48	33	27
Control	88	79	51	28	16



0	180	360	540	730
61	55	46	32	25
88	72	51	36	23

FIGURE 3 Outcomes of AF Ablation

Kaplan-Meier curves for single-procedure, drug-free, AF-free survival **(left)** and for total AF-free survival (multiple procedures ± drugs) **(right)**. Curves for 2 years are provided, after which <20% of patients completed follow-up. Note that data are provided after the last procedure using a 3-month blanking period. RFM = risk factor management; other abbreviation as in Figure 1.

follow-up, arrhythmia-free survival rates after the last catheter ablation procedure were 87% with RFM compared with 17.8% for the control group ($p < 0.001$). Univariate predictors of AF recurrence after multiple procedures were: control group (HR: 6.2 [95% CI: 2.6 to 14.5]; $p < 0.001$); type of AF (nonparoxysmal AF: HR: 3.3 [95% CI: 1.8 to 5.9]; $p < 0.001$); and poor BP control, evidenced by the number of antihypertensive medications (HR: 1.3 [95% CI: 1.03 to 1.64]; $p = 0.02$). Patient group (HR: 4.8 [95% CI: 2.04 to 11.4]; $p < 0.001$) remained the most significant predictor of recurrent AF in multivariate analyses. Online Figure 1 displays the differences in outcome on the basis of AF type.

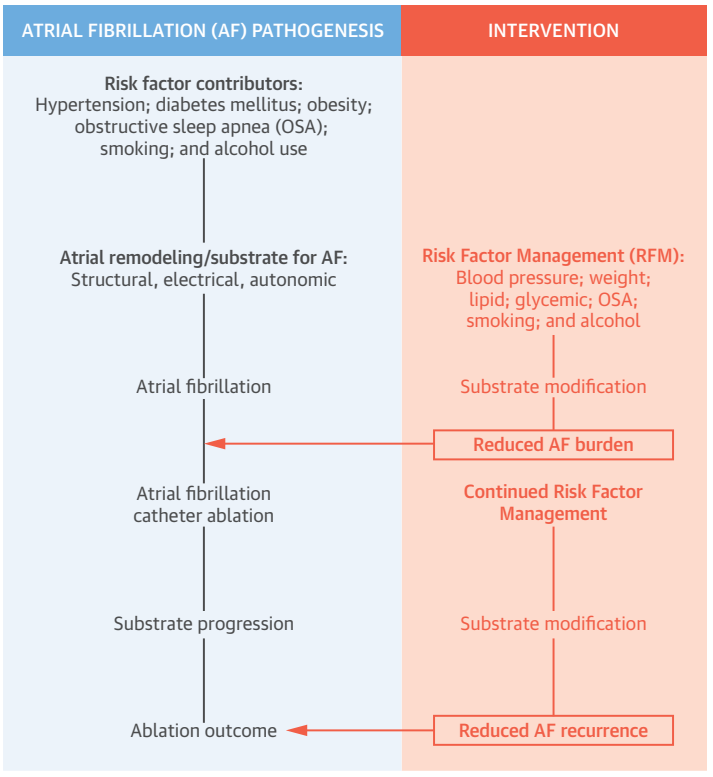
DISCUSSION

This study found that in patients with highly symptomatic AF undergoing ablation, a structured physician-directed risk factor and weight management program resulted in significant improvement in the long-term outcomes. These effects were associated with structural remodeling, with significant improvement in LA volumes and LV hypertrophy. The findings emphasize the importance of treating the underlying causes of AF to achieve rhythm control and maintenance of sinus rhythm.

Catheter ablation is an effective therapy for rhythm control in patients with drug-refractory or intolerant AF. Despite recent advances in ablative techniques, long-term outcomes post-ablation have not improved proportionately, especially in those with more persistent forms of the arrhythmia (25). Updates from several centers confirm the need for multiple procedures, which, in general, have occurred early (13,14,26) and are related to incomplete ablation during previous efforts with residual pulmonary vein conduction (27,28). More concerning is that, despite further ablation and a period without arrhythmia, progressive attrition in success is observed with time (13,14,18). This late recurrence was proposed to also be due to persistent pulmonary vein conduction (27,28). However, it seems unusual that recovery of pulmonary vein conduction, which would be expected to occur early, would contribute to delayed recurrence of arrhythmia. Several single-center experiences identified a variety of cardiac risk factors that were more frequently present in patients with late recurrence of AF (19,20,29,30).

Cardiac risk factors such as hypertension, DM, obesity, and OSA have been independently shown to increase the incidence of AF (4-6,31). Importantly, these cardiac risk factors are associated with structural and electrical remodeling of the atria that forms the substrate leading to AF development and progression (32-34). Indeed, even in the absence of known risk factors, atrial changes consistent with the AF substrate have been observed in "lone AF" patients (23). Several studies allude to further evidence of the importance of an underlying substrate to the progression of AF. It was postulated that early cardioversion would prevent remodeling due to AF and allow "sinus rhythm to beget sinus rhythm"; however, restoration of sinus rhythm reversed electrical remodeling but did not affect sinus rhythm maintenance (35). Finally, in a recent study, a progressive atrial substrate was observed, even after successful catheter ablation of AF (26). These findings argue in favor of an underlying atrial substrate responsible for AF, which is promoted by inadequately treated or unrecognized risk factors.

Upstream therapy has been demonstrated to reduce AF. Antihypertensive therapy reduces LA size



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CENTRAL ILLUSTRATION Impact of Risk Factor and Weight Management on AF Ablation Outcomes

The schematic demonstrates the natural progression of the atrial fibrillation (AF) substrate and its impact on the maintenance of sinus rhythm **(blue)**. Risk factor management has been demonstrated to reduce the burden of AF and also improve the outcomes of catheter ablation **(salmon)**.

and LV hypertrophy, leading to a lower risk of AF (36). Angiotensin receptor blockade in conjunction with cardioversion reduces the recurrence of AF (37). In mitral stenosis, treatment of the primary cause reversed the abnormal atrial substrate (38). A recent study observed that weight and cardiometabolic RFM in overweight individuals with AF resulted in a reduction of the AF symptom burden (39). In the setting of AF ablation, emerging data showed that CPAP for OSA was associated with higher ablation success (29).

The present study extends these observations by demonstrating markedly improved outcomes of maintaining sinus rhythm by addressing each of the risk factors that potentially contributed to AF development and, therefore, to the underlying atrial substrate. The results are so striking that concurrent risk factor treatment seems an essential component of strategies for rhythm control in patients with AF (**Central Illustration**).

STUDY LIMITATIONS. This study was a single-center, observational study and requires confirmation in a randomized controlled trial to minimize the potential for selection bias and better control of confounders. Finally, we targeted each risk factor, treating to recommended targets. As a result, this study does not provide insight into the relative contribution of each risk factor or variable treatment targets.

CONCLUSIONS

RFM significantly improved the outcomes of AF ablation by reducing AF burden and severity in conjunction with favorable changes in cardiac remodeling in these study patients. The findings underscore the importance of therapy directed at the primary promoters of the AF substrate to facilitate a rhythm control strategy in patients with AF.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Prashanthan Sanders, Centre for Heart Rhythm Disorders, Department of Cardiology, Royal Adelaide Hospital, L5 McEwin Building, North Terrace, Adelaide 5000, Australia. E-mail: prash.sanders@adelaide.edu.au.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Recurrence of AF during long-term follow-up after catheter-based ablation is due to progression of underlying atrial pathology.

COMPETENCY IN PATIENT CARE: Control of risk factors (including excessive body weight) is an important component of a rhythm control strategy for patients with AF.

TRANSLATIONAL OUTLOOK: Further studies are needed to clarify the mechanisms by which obesity is related to the progression of the atrial pathology associated with recurrent or refractory AF.

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KEY WORDS cardiac risk factors, catheter ablation, follow-up studies, obesity, outcomes remodeling

APPENDIX For a supplemental figure, please see the online version of this article.