Original Investigation

Effect of Weight Reduction and Cardiometabolic Risk Factor Management on Symptom Burden and Severity in Patients With Atrial Fibrillation

A Randomized Clinical Trial

Hany S. Abed, BPharm, MBBS; Gary A. Wittert, MBBch, MD; Darryl P. Leong, MBBS, MPH, PhD; Masoumeh G. Shirazi, MD; Bobak Bahrami, MBBS; Melissa E. Middeldorp; Michelle F. Lorimer, BSc; Dennis H. Lau, MBBS, PhD; Nicholas A. Antic, MBBS, PhD; Anthony G. Brooks, PhD; Walter P. Abhayaratna, MBBS, PhD; Jonathan M. Kalman, MBBS, PhD; Prashanthan Sanders, MBBS, PhD

IMPORTANCE Obesity is a risk factor for atrial fibrillation. Whether weight reduction and cardiometabolic risk factor management can reduce the burden of atrial fibrillation is not known.

OBJECTIVE To determine the effect of weight reduction and management of cardiometabolic risk factors on atrial fibrillation burden and cardiac structure.

DESIGN, SETTING, AND PATIENTS Single-center, partially blinded, randomized controlled study conducted between June 2010 and December 2011 in Adelaide, Australia, among overweight and obese ambulatory patients (N = 150) with symptomatic atrial fibrillation. Patients underwent a median of 15 months of follow-up.

INTERVENTIONS Patients were randomized to weight management (intervention) or general lifestyle advice (control). Both groups underwent intensive management of cardiometabolic risk factors.

MAIN OUTCOMES AND MEASURES The primary outcomes were Atrial Fibrillation Severity Scale scores: symptom burden and symptom severity. Scores were measured every 3 months from baseline to 15 months. Secondary outcomes performed at baseline and 12 months were total atrial fibrillation episodes and cumulative duration measured by 7-day Holter, echocardiographic left atrial area, and interventricular septal thickness.

RESULTS Of 248 patients screened, 150 were randomized (75 per group) and underwent follow-up. The intervention group showed a significantly greater reduction, compared with the control group, in weight (14.3 and 3.6 kg, respectively; $P < .001$) and in atrial fibrillation symptom burden scores (11.8 and 2.6 points, $P < .001$), symptom severity scores (8.4 and 1.7 points, $P < .001$), number of episodes (2.5 and no change, $P = .01$), and cumulative duration (692-minute decline and 419-minute increase, $P = .002$). Additionally, there was a reduction in interventricular septal thickness in the intervention and control groups (1.1 and 0.6 mm, $P = .02$) and left atrial area (3.5 and 1.9 cm^2, $P = .02$).

CONCLUSIONS AND RELEVANCE In this study, weight reduction with intensive risk factor management resulted in a reduction in atrial fibrillation symptom burden and severity and in beneficial cardiac remodeling. These findings support therapy directed at weight and risk factors in the management of atrial fibrillation.

TRIAL REGISTRATION anzctr.org.au Identifier: ACTRN12610000497000

JAMA. 2013;310(19):2050-2060. doi:10.1001/jama.2013.280521

Author Audio Interview at jama.com

Supplemental content at jama.com

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Prashanthan Sanders, MBBS, PhD, Center for Heart Rhythm Disorders, Department of Cardiology, Royal Adelaide Hospital, Adelaide, South Australia, Australia 5000 (prash.sanders@adelaide.edu.au).

Atrial fibrillation has been described as the epidemic of the new millennium,[1] with a projection that by 2050 there will be 12 million to 15 million affected individuals in the United States.[2] In the United States, the direct economic cost of atrial fibrillation is estimated at $6 billion annually.[3] Although population aging is regarded as an important contributor, obesity may account for a substantial proportion of the increasing prevalence.[4]

Obesity has been associated with diastolic dysfunction,[5] a systemic proinflammatory state,[6] autonomic tone abnormalities,[7] and atrial enlargement[8]—changes known to promote arrhythmogenesis.[9] In addition, fat stores have been shown to correlate with incident atrial fibrillation.[10] A recent study has demonstrated a direct effect of obesity on the atrial substrates.[11] We therefore evaluated the effect of a structured weight reduction and risk factor management program on atrial fibrillation burden in a randomized controlled trial.

Methods

Study Population

Patients were recruited from the Centre for Heart Rhythm Disorders at the University of Adelaide, Adelaide, Australia. Inclusion criteria were symptomatic paroxysmal or persistent atrial fibrillation (in sinus rhythm at enrollment); body mass index (BMI) greater than 27 (calculated as weight in kilograms divided by meters squared); waist circumference greater than 100 cm (men) or greater than 90 cm (women); and age 21 to 75 years. Exclusion criteria included recent participation (within 3 months) in a weight loss program; unstable international normalized ratio (INR); diabetes necessitating insulin; significant cardiac valvular disease, and inability to provide informed consent (details in eTable 1 in Supplement). Patients were censored if they underwent ablation of atrial fibrillation or atrioventricular-node ablation.

All patients provided written informed consent to the study protocol approved by the human research ethics committee of the Royal Adelaide Hospital and the University of Adelaide.

Study Protocol and Design

This single-center, partially blinded, randomized controlled trial, with a median 15-months' follow-up, randomized patients to either a physician-led weight loss program (intervention group) or to self-directed general lifestyle measures (control group). Both groups underwent intensive management of cardiometabolic risk factors. A software-based obesity management system (OBEMAN) developed at the University of Adelaide was used to assess and monitor patients undergoing a tailored weight loss program. Patients were evaluated at 3-month intervals.

Study Blinding

Study coordinators, treating physicians, and other personnel, with the exception of weight loss counselors, were blinded to randomization, and patients were instructed not to disclose their status. Patient records contained generic statements without indicating group allocation.

Weight Management

Intervention Group | The 2 phases of the program, weight loss and weight maintenance, followed a previously described approach.[12]

Weight loss was induced over 8 weeks using a modified very-low-calorie diet (800-1200 kcal/d). Patients were prescribed very-low-calorie meal replacement sachets (Prima Health Solutions) for 2 of their daily meals. The third meal consisted of calorie-controlled foods with high levels of animal and plant proteins and low glycemic index. A written exercise plan prescribed low-intensity exercise (walking or cycling), initially for 20 minutes 3 times weekly and then increasing to 45 minutes 3 times weekly.

Very low-calorie meals were gradually phased out and replaced with low-glycemic index meals, exercise intensity uptitration, and behavioral modification,[13] for the following 13 months. Goal-directed face-to-face clinic visits were scheduled every 3 months. Participants scheduled additional visits as required and were provided 24-hour e-mail and telephone support.

Participants in the intervention group were required to maintain a diet, activity, and blood pressure diary.

Control Group | Written and verbal nutrition and exercise advice was provided at enrollment. Fish oil (3 g/d) was prescribed except for participants taking dual antiplatelet agents or oral anticoagulants. Completion of a diet and activity diary was not requested.

Outcomes

The primary outcome was atrial fibrillation symptom burden, quantified using the Atrial Fibrillation Severity Scale (AFSS) (eFigure 9 in Supplement). 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 atrial fibrillation: event frequency (scored 1-10), duration (scored 1.25-10), and global episode severity (scored 1-10).[14] In addition, the AFSS assesses symptom severity via an associated symptom-specific continuous subscale (range, 0 [no symptoms] to 35 [severe symptomatology]). The secondary outcomes were 7-day Holter-derived atrial fibrillation episode and duration burden, echocardiographic left atrial area, and left ventricular wall thickness.

Anthropometry

A stadiometer and digital scales were used to record height and weight in light clothing without shoes. Waist circumference was measured at the midpoint between the iliac crest and the lowest rib, and BMI was calculated. Anthropometric values were measured at 3-month intervals.

Management of Cardiometabolic Risk Factors

Hypertension, hyperlipidemia, glucose intolerance, sleep apnea, and alcohol and tobacco use were screened for and managed in both groups.

If fasting glucose level was between 100 mg/dL (5.55 mmol/L) and 125 mg/dL (6.94 mmol/L), a 2-hour oral glucose

tolerance test was performed. Impaired glucose tolerance was managed with lifestyle measures. Metformin was added if diabetes was present. Patients with poor glycemic control (glycated hemoglobin level >7%) were referred to a diabetes clinic.

Hyperlipidemia was managed by combining lifestyle measures, HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors, and fibrates to achieve target values outlined in the National Cholesterol Education Program.[15]

Patients were asked to measure blood pressure 2 to 3 times daily at home using an appropriately sized cuff. For each recording, measurements were performed 3 times, and the mean was recorded. Hypertension was treated using renin-angiotensin-aldosterone system antagonists preferentially. Other agents were added to achieve a resting blood pressure less than 130/90 mm Hg. Ambulatory blood pressure monitoring (24-hour) was performed if home and clinic measurements were discrepant. Changes in pharmacotherapy were recorded at each visit. Fasting blood was drawn at enrollment and follow-up for measurement of serum lipids, C-reactive protein (CRP), insulin, and glucose levels, using previously described methods.[16]

All patients underwent laboratory-based polysomnography, with scoring using standard criteria.[17,18] Patients with moderate-severe obstructive sleep apnea (apnea-hypopnea index >30 episodes/h) were offered continuous positive airway pressure. Those with an apnea-hypopnea index of 15 episodes/h to 30 episodes/h were offered treatment based on the degree of hypersomnolence, cardiovascular risk, and nocturnal oxygen desaturation.

Written and verbal counseling was provided for smoking cessation and alcohol reduction. An ultimate goal of alcohol reduction (≤30 g/wk) or abstinence was set a priori.

Antiarrhythmic Pharmacotherapy

Antiarrhythmic agents were prescribed for rate control, rhythm control, or both at the discretion of the treating physician. Changes were documented at each visit.

Atrial Fibrillation

The AFSS questionnaire was administered at baseline and 3-month intervals. Holter recordings were obtained at baseline and repeated at 12 months. Analysis was performed by 2 independent scientists blinded to participant randomization. Any episode of atrial arrhythmia lasting 30 seconds or longer was considered atrial fibrillation. Total duration of atrial fibrillation was the cumulative sum of all discrete episodes.

Cardiac Structure

Transthoracic echocardiography was performed with a 3.5-MHz probe (Vivid7, GE Medical Systems) at baseline and at 12-month follow-up to measure left atrial area and left ventricular wall thickness. Left ventricular mass was calculated from the posterior wall thickness, septal wall thickness, and left ventricular end-diastolic dimension as recommended by the American Society of Echocardiography.[19] Data were stored digitally and analyzed offline (EchoPac PC version 8 2009, GE Health Care) by an experienced cardiologist blinded to randomization.

Statistical Analysis

Sample Size Calculation and Study Power

Singh et al[20] compared quality of life and atrial fibrillation symptom burden between rate and rhythm control strategies. A group with sinus rhythm maintenance had a mean baseline BMI of 30.5 (SD, 5.6) and a mean baseline AFSS symptom burden score of 13.3 (SD, 7.3); corresponding values in a group with persistent atrial fibrillation were 32.4 (SD, 6.0) and 13.5 (SD, 6.6), respectively. A mean reduction of 7.6 in the absolute atrial fibrillation symptom burden score resulted in clinically meaningful benefits in the group with sinus rhythm maintenance. Therefore, we estimated a baseline atrial fibrillation burden score of 13 in each group. In addition, with the anticipation of a worst-case-scenario 35% attrition rate,[21] enrolling 178 patients would achieve 85% power to detect a 30% difference in atrial fibrillation symptom burden score between groups at last follow-up, for a 2-sided α of .05. Eligible patients were randomized in a 1:1 ratio to either group using SPSS version 17 (IBM SPSS Inc).

Data Analysis

Differences in outcomes were determined within each group and between the 2 study groups on an intention-to-treat basis. Continuous variables are presented as mean and 95% CI or mean and standard deviation (SD) when normally distributed on visual inspection of their histograms and as median (interquartile range) when not normally distributed. Categorical variables are summarized as count (proportion). For repeated-measures analysis of continuous dependent variables, mixed-effects modeling was used, with patient identity included as a random effect. Randomization group was entered into the mixed model as part of an interaction term with patients' visit time. If this group × time interaction term was significant, it was retained in the model, implying that the influence of randomization group on the outcome variable was time dependent. Post hoc testing was performed to determine whether the group influence on the dependent variable was significant at each visit.

For repeated-measures analysis of binary and nonnormal dependent variables, an analogous approach was adopted using generalized estimating equations. A binomial probability distribution with logit link function or a Poisson distribution with log link function were assumed as appropriate, as was an autoregressive correlation structure. Post hoc logistic regression was used to determine whether group allocation was predictive of subsequent need for radiofrequency catheter ablation.

To account for atrial fibrillation ablations performed on participants, we performed sensitivity analyses, because these procedures may be regarded as a clinically relevant outcome and may alter the burden of atrial fibrillation in a given individual. In the first sensitivity analysis, AFSS scores and Holter data were imputed to baseline values for the time points following the ablation. In the second sensitivity analysis, these variables were imputed to the preablation value. In the third analysis, those control participants who underwent ablation of atrial fibrillation were excluded. To

determine the influence of dropouts on the study findings, a further sensitivity analysis was performed. For AFSS scores, differences between final and baseline scores were regressed against patient randomization group as a predictor variable. We determined the effect on the regression coefficients of varying the missing AFSS scores in the intervention group, the control group, or both. The range of the sensitivity analysis encompassed 1 SD of the AFSS score variable. For Holter data we used a binary end point of freedom from atrial fibrillation.

All statistical tests were 2-sided, and $P < .05$ was considered statistically significant. Analyses were performed using STATA version 12.1 (Stata Corp).

Results

Study Participants, Baseline Characteristics, and Follow-up

Of consecutive patients with a BMI greater than 27 (n = 248), 178 were eligible and provided consent. Of these, 28 (10 in the intervention group and 18 in the control group) withdrew prior to the program initiation. The final cohort therefore included 150 patients; 75 in the intervention group and 75 in the control group (**Figure 1**). Mean follow-up was 12.9 (95% CI, 12.3-13.5) months in the intervention group and 12.0 (95% CI, 11.1-12.9) months in the control group (median, 15 months for both groups). At 12 months, 109 (73%) had completed the study (57 in the intervention group and 52 in the control group). By 15 months, 81 (54%) remained (42 in the intervention group and 39 in the control group). Of the 69 not completing 15 months' follow-up, 23 underwent catheter ablation (10 in the intervention group [6 at 12 months and 3 at 15 months] and 14 in the control group [6 at 9 months, 2 at 12 months, and 6 at 15 months]). One patient in the intervention group underwent atrioventricular-node ablation and pacemaker implantation at 15 months. Patients undergoing ablation were removed from further analysis immediately after undergoing the procedure. Baseline characteristics were similar in both groups (**Table 1**).

Anthropometrics

Weight, BMI, and waist circumference decreased in both groups but significantly more in the intervention group (**Table 2**). Differences were evident by 3 months and persisted for the remainder of follow-up; $P < .001$ for group × time interaction for all measures (**Figure 2** and eFigure 1 in Supplement).

Atrial Fibrillation

Atrial Fibrillation Severity

Atrial fibrillation symptom burden and symptom severity scores all declined in both the intervention and the control groups ($P \leq .01$, both domains) (Table 2, **Figure 3**, and eFigure 2 in Supplement). No significant change was observed from baseline to 3 months in atrial fibrillation symptom burden (intervention group: 21.0 [95% CI, 20.1-21.9] to 19.6 [95% CI, 18.4-20.9]; control group: 21.6 [95% CI, 20.5-22.7] to 21.0 [95% CI, 19.8-22.3]; $P = .21$) or symptom severity (intervention group: 15.2 [95% CI, 13.6-16.8] to 14.1 [95% CI, 12.3-15.8]; control group: 16.0 [95% CI, 14.3-17.7] to 15.7 [95% CI, 14.1-17.3]; $P = .24$) (eTable 2 in Supplement). From 6 months to 15 months the intervention group showed greater decline in both domains, relative to the control group (burden score, 21.0 [95% CI, 20.1-21.9] to 8.8 [95% CI, 7.6-10.1] for the intervention group and 21.6 [95% CI, 20.5-22.7] to 18.7 [95% CI, 16.7-20.6] for the control group; symptom score, 15.2 [95% CI, 13.6-16.8] to 6.7 [95% CI, 5.0-8.4] for the intervention group and 16.0 [95% CI, 14.3-17.7] for the control group; group × time interaction for both domains, $P < .001$) (Figure 3). Secondary analysis for AFSS symptom frequency, duration, and global episode severity scores showed significantly greater decline in the intervention group compared with the control group (group × time interaction, $P < .001$ for all 3 subscales) (Table 2 and eFigure 2 in Supplement).

Continuous Rhythm Monitoring

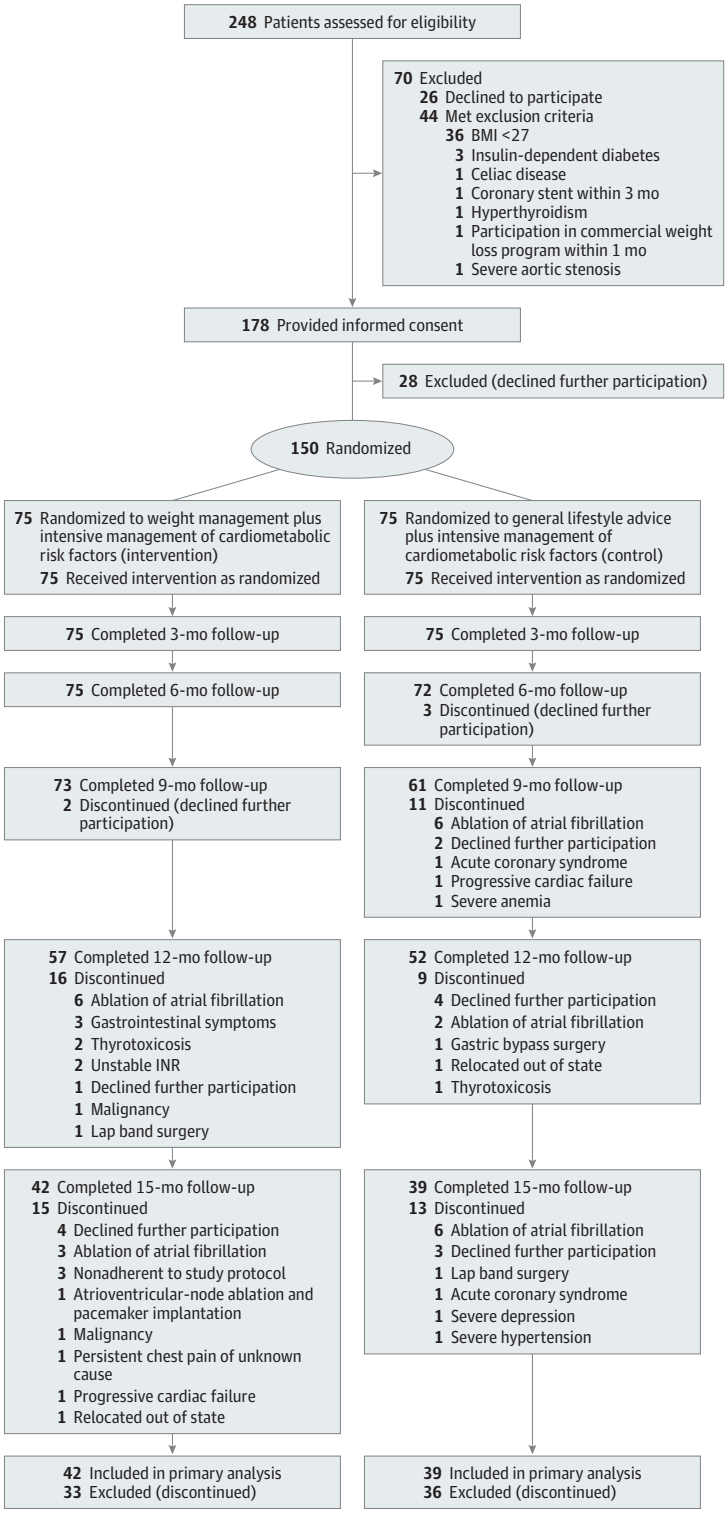
Holter recordings were undertaken at baseline and at 12 months among 109 patients (57 in the intervention group, 52 in the control group) (Tables 1 and 2). The mean number of atrial fibrillation episodes in the intervention group decreased from 3.3 (95% CI, 1.6-4.9) to 0.62 (95% CI, 0.19-1.0), and the duration of atrial fibrillation decreased from 1176 (95% CI, 720-1632) minutes to 491 (95% CI, 159-822) minutes. In the control group, the mean number of atrial fibrillation episodes was 2.8 (95% CI, 1.7-4.0) at baseline and 2.0 (95% CI, 1.1-3.0) at 12 months, and the duration of atrial fibrillation increased from 1393 (95% CI, 785-1994) minutes to 1546 (95% CI, 782-2308) minutes. Both measures showed significant group differences (group × time interaction, $P < .001$). After adjustment for baseline BMI, duration of atrial fibrillation disease, longest atrial fibrillation episode, and atrial fibrillation type, the probability of having 1 or more atrial fibrillation episodes between baseline and follow-up remained lower in the intervention group (0.6 [95% CI, 0.5-0.7] to 0.2 [95% CI, 0.1-0.3]) compared with the control group (0.6 [95% CI, 0.5-0.7] to 0.5 [95% CI, 0.4-0.6]), with a significant group × time interaction ($P < .001$).

Cardiac Structure

From baseline to 12 months, height-indexed left atrial area decreased from 13.5 (95% CI, 12.9-14.1) cm^2m^{-1} to 11.5 (95% CI, 11.0-12.1) cm^2m^{-1} in the intervention group ($P < .001$) and from 14.0 (95% CI, 13.4-14.6) cm^2m^{-1} to 12.9 (95% CI, 12.2-13.6) cm^2m^{-1} in the control group ($P < .001$), with a significant group × time interaction ($P = .01$). Height-indexed left atrial volume decreased from 39.4 (95% CI, 36.9-41.9) mLm^{-1} to 34.3 (95% CI, 31.9-36.6) mLm^{-1}) ($P < .01$) in the intervention group and from 41.5 (95% CI, 38.9-44.1) mLm^{-1} to 37.7 (95% CI, 34.6-40.9) mLm^{-1} in the control group ($P = .19$), with a group × time interaction of $P = .20$. Septal thickness decreased in both the intervention group (11.3 [95% CI, 11.0-11.7] mm to 10.2 [95% CI, 9.8-10.6] mm, $P < .001$) and the control group (11.5 [95% CI, 11.0-11.9] mm to 10.8 [95% CI, 10.4-11.2] mm, $P < .001$), with a group × time interaction of $P = .01$. Posterior wall thickness also decreased more in the intervention group (10.3 [95% CI, 10.0-10.6] mm to 9.2 [95% CI, 8.9-9.4] mm, $P < .001$) than in the con-

trol group (10.1 [95% CI, 9.8-10.5] mm to 9.8 [95% CI, 9.5-10.2] mm, $P < .001$), with a group × time interaction of $P < .001$. Height-indexed left ventricular mass decreased from 1.1 (1.1-1.2) g^{-1} to 0.9 (0.9-1.0) g^{-1} in the intervention group ($P < .001$) and from 1.2 (95% CI, 1.1-1.3) g^{-1} to 1.1 (95% CI, 1.0-1.2) g^{-1} in the control group ($P = .23$), with a group × time interaction of $P < .01$. The complete echocardiographic findings are reported in eTable 4 in Supplement.

Figure 1. Patient Recruitment, Attrition, and Retention



BMI indicates body mass index; INR, international normalized ratio.

Table 1. Baseline Characteristics of Study Groups

Characteristic	Intervention (n = 75)	Control (n = 75)
Age, mean (SD), y	59.8 (9.5)	60.3 (10.3)
Men, No. (%)	51 (68)	50 (67)
Anthropometric measures, mean (SD)		
Waist circumference, cm	110.1 (9.5)	112.2 (10.9)
Weight, kg	98.8 (13.1)	101.4 (16.4)
BMI[a]	32.8 (3.5)	33.8 (4.1)
BSA, m^2[b]	2.1 (0.2)	2.2 (0.2)
Metabolic risk factors, No. (%)		
Excess alcohol consumption (>30 g/wk)	26 (35)	26 (35)
Smoker		
No	43 (57)	45 (60)
Current	2 (3)	5 (7)
Reformed	30 (40)	25 (33)
Hypertension	62 (83)	65 (87)
Diabetes mellitus/impaired glucose tolerance	18 (24)	21 (28)
Hyperlipidemia	45 (60)	51 (68)
Coronary artery disease	7 (9)	10 (13)
Valvular heart disease	5 (7)	4 (5)
Obstructive sleep apnea	55 (89)	52 (84)
Moderate-severe apnea	30 (48)	32 (52)
AHI (95% CI)	22.8 (19.3-26.3)	23.5 (19.3-27.6)
Medication use, No. (%)		
No. of antiarrhythmic agents		
0	6 (8)	2 (3)
1	40 (53)	42 (56)
2	29 (39)	31 (41)
No. of antihypertensive agents		
0	12 (16)	17 (23)
1	37 (49)	27 (36)
2	17 (23)	17 (23)
3	6 (8)	10 (13)
4	3 (4)	4 (5)
Echocardiographic measures, mean (95% CI)		
Left atrial		
Area, cm^2	23.4 (22.4-24.4)	24.2 (23.1-25.3)
Area indexed, cm^2m^{-1}	13.5 (12.9-14.1)	14.0 (13.4-14.5)
Left ventricular		
Septum, mm	11.3 (11.0-11.7)	11.5 (11.0-11.9)
Posterior wall, mm	10.3 (10.0-10.6)	10.1 (9.8-10.4)
End-diastolic diameter, mm	48.2 (47.0-49.4)	48.2 (46.9-49.5)
Mass, g	193.0 (183.1-202.8)	194.0 (181.6-206.3)
Mass indexed, g^{-1}	1.1 (1.0-1.2)	1.2 (1.1-1.3)
Paroxysmal AF	44 (59)	42 (56)
AFSS scores, mean (95% CI)[c]		
Symptom burden	21.0 (20.1-21.9)	21.6 (20.5-22.7)
Episode frequency	7.1 (6.6-7.5)	7.4 (6.8-7.9)
Episode duration	7.1 (6.6-7.5)	7.4 (6.8-7.9)
Global episode severity	6.8 (6.3-7.4)	6.9 (6.4-7.4)
Symptom severity	15.2 (13.6-16.8)	16.0 (14.3-17.7)
Duration of AF, mo (95% CI)	72 (57-87)	89 (68-108)
Longest episode, h (95% CI)	79 (40-118)	54 (34-74)
Ambulatory recording (95% CI)		
Continuous duration, h	76 (67-84)	77 (67-86)
No. of AF episodes ≥30 s[d]	3.3 (1.6-4.9)	2.8 (1.7-4.0)
Cumulative AF duration, min	1176 (720-1632)	1394 (795-1994)

Abbreviations: AF, atrial fibrillation; AFSS, Atrial Fibrillation Severity Scale; AHI, apnea-hypopnea index; BMI, body mass index; BSA, body surface area.

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

[b] From Mosteller estimation method.

[c] Ranges of possible scores: 3.25 to 30 for symptom burden; 1 to 10 for episode frequency; 1.25 to 10 for episode duration; 1 to 10 for global episode severity; 0 to 35 for symptom severity. Symptom burden score comprises the arithmetic sum of the 3 subscores.

[d] Recorded over a 7-day continuous ambulatory rhythm recording.

Table 2. Anthropometric Measures, Serum Biochemistry Values, Blood Pressure, and Atrial Fibrillation Frequency and Duration at Baseline and Follow-up

Variable	Mean (95% CI)				P Value[b]
	Intervention		Control		
	Baseline (n = 75)	Follow-up[a] (n = 42)	Baseline (n = 75)	Follow-up[a] (n = 39)	
Anthropometric measures					
Waist circumference, cm	110 (108 to 112)	92.8 (89.5 to 96.1)	112 (110 to 114)	107 (103 to 111)	<.001
Weight, kg	99 (96 to 102)	80 (76 to 84)	101 (97 to 105)	96 (90 to 102)	<.001
BMI[c]	32.8 (32.0 to 33.6)	27.2 (26.3 to 28.1)	33.8 (32.9 to 34.7)	32.5 (31.1 to 33.9)	<.001
Serum biochemistry, blood pressure					
Glucose, mg/dL	104.9 (99.0 to 110.9)	96.5 (90.5 to 102.6)	103.9 (98.8 to 108.9)	100.4 (94.5 to 106.4)	.30
Insulin, μIU/mL	33.9 (29.7 to 38.1)	13.5 (11.6 to 15.5)	33.7 (30.4 to 37.1)	21.2 (17.9 to 24.4)	.004
Triglycerides, mg/dL	137 (122 to 150)	115 (99 to 131)	142 (127 to 157)	138 (115 to 161)	.08
Total cholesterol, mg/dL	178 (168 to 188)	169 (158 to 179)	188 (177 to 199)	176 (162 to 189)	.50
HDL-C, mg/dL	45 (42 to 48)	50 (46 to 54)	46 (43 to 49)	48 (44 to 53)	.10
LDL-C, mg/dL	110 (101 to 119)	98 (89 to 107)	118 (108 to 128)	103 (91 to 115)	.80
hsCRP, mg/L	2.5 (2.1 to 2.9)	1.3 (1.0 to 1.5)	2.3 (1.9 to 2.6)	1.9 (1.4 to 2.3)	<.001
Blood pressure, mm Hg					
Systolic	136 (133 to 139)	133 (130 to 135)	137 (133 to 140)	136 (132 to 139)	<.001
Diastolic	82 (81 to 84)	80 (78 to 81)	84 (82 to 86)	83 (81 to 85)	.02
AFSS score, change from baseline to last follow-up[d]					
Symptom burden	11.8 (10.0 to 13.6)		2.6 (0.8 to 4.3)		<.001
Episode frequency score	3.4 (2.8 to 4.0)		0.7 (0.2 to 1.2)		<.001
Episode duration score	5.0 (4.3 to 5.7)		0.8 (−0.1 to 1.8)		<.001
Global episode severity score	3.4 (2.6 to 4.2)		1.0 (0.3-1.8)		<.001
Symptom severity score	8.4 (5.9 to 10.9)		1.7 (−0.5 to 3.9)		<.001
Atrial fibrillation detected by 7-d continuous ambulatory rhythm recording					
	n = 75	n = 57	n = 75	n = 52	
≥1 episode, No. (%)	49 (65)	9 (21)	43 (57)	22 (56)	<.001
No. of episodes	3.3 (1.6 to 4.9)	0.62 (0.19 to 1.0)	2.8 (1.7 to 4.0)	2.0 (1.1 to 3.0)	<.001
Total duration, min	1176 (720 to 1632)	491 (159 to 822))	1394 (795 to 1994)	1546 (782 to 2308)	<.001

Abbreviations: AFSS, Atrial Fibrillation Severity Scale; BMI, body mass index; hsCRP, high-sensitivity C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

SI conversion factors: To convert glucose values to mmol/L, multiply by 0.0555; insulin values to pmol/L, multiply by 6.945; triglyceride values to mmol/L, multiply by 0.0113; total cholesterol, HDL-C, and LDL-C values to mmol/L, multiply by 0.0259; and CRP values to nmol/L, multiply by 9.524.

[a] Median follow-up, 15 months for both groups.

[b] *P* value refers to between group differences over time (group × time interaction).

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

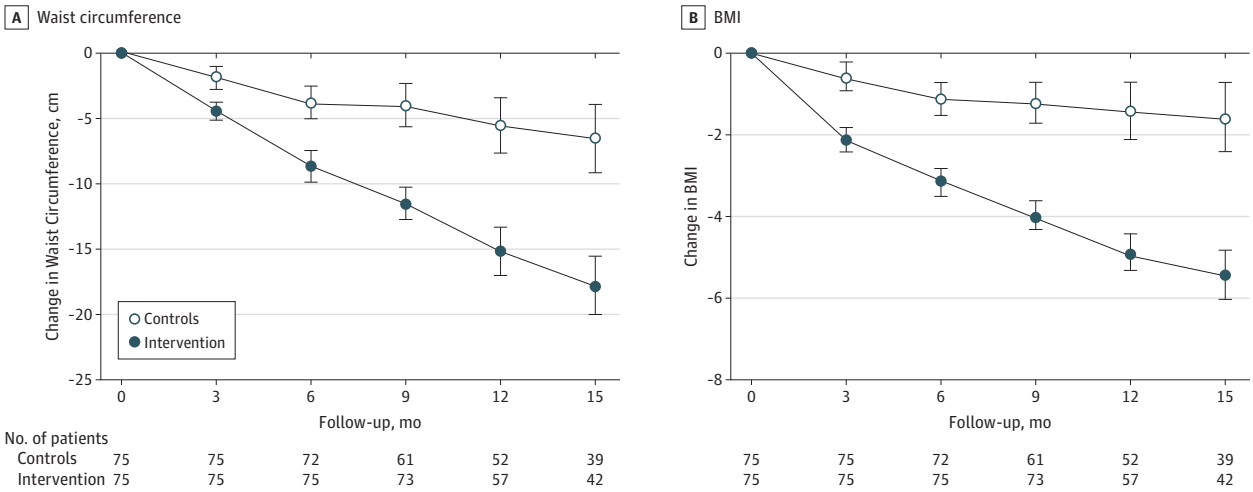
[d] Ranges of possible scores: 3.25 to 30 for symptom burden; 1 to 10 for episode frequency; 1.25 to 10 for episode duration; 1 to 10 for global episode severity; 0 to 35 for symptom severity. Symptom burden score comprises the arithmetic sum of the 3 subscores.

Intervention Uptake, Pharmacotherapy, and Risk Factor Modification

From enrollment to study conclusion there was an increase in patients consuming fish oil (controls, 3 to 55), metformin (intervention group, 1 to 15; control group, 2 to 11), and hypolipidemic agents (intervention group, 16 to 44; control group, 23 to 44) and an increase in use of continuous positive airway pressure (intervention group, 5 to 21; control group, 7 to 23) (eFigure 3 in Supplement) (*P* < .001 for all interventions in both groups). There was a decrease in numbers of patients with elevated blood pressure (intervention group, 64 to 16; control group, 67 to 44), elevated lipid levels (intervention group, 51 to 13; control group, 58 to 30), and alcohol consumption greater than 30 g/wk (intervention group, 25 to 4; control group, 28 to 16) (*P* < .001 for all risk factors in both groups).

There was a greater decline in excessive alcohol consumption as defined a priori in the intervention group than in the control group (*P* = .01). There was a reduction in systolic and diastolic blood pressure in the intervention group (from 136 [95% CI, 134-139] mm Hg systolic and 82 [95% CI, 81-84] mm Hg diastolic at baseline to 133 [95% CI, 130-136] mm Hg systolic and 80 [95% CI, 78-82] mm Hg diastolic at 15 months, *P* < .001 for both systolic and diastolic) but little change in the control group (from 137 [95% CI, 133-140] mm Hg systolic and 84 [95% CI, 82-86] mm Hg diastolic at baseline to 136 [95% CI, 132-139] mm Hg systolic and 83 [95% CI, 81-85] mm Hg diastolic at 15 months, *P* = .05 for systolic and *P* = .03 for diastolic), with a significant effect of group allocation at 15 months (*P* < .001 for systolic and *P* = .02 for diastolic). Use of antihypertensive agents

Figure 2. Changes in Waist Circumference and Body Mass Index From Baseline (Enrollment) to 15 Months' Follow-up

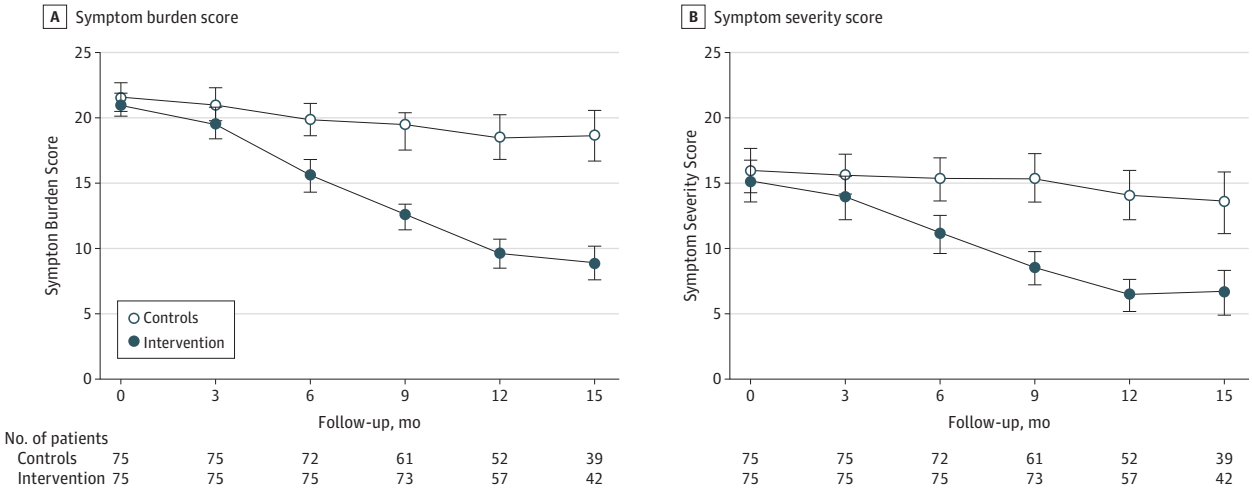


No. of patients

Controls	75	75	72	61	52	39
Intervention	75	75	75	73	57	42

Error bars indicate 95% confidence intervals. BMI indicates body mass index, calculated as weight in kilograms divided by height in meters squared. A, Between-group level of significance: $P = .21$ at time 0, $P = .01$ at 3 months, $P < .001$ at 6, 9, 12, and 15 months. B, Between-group level of significance: $P = .13$ at time 0, $P < .001$ at 3, 6, 9, 12, and 15 months.

Figure 3. Changes in Atrial Fibrillation Symptom Scale (AFSS) Scores Over Study Follow-up



No. of patients

Controls	75	75	72	61	52	39
Intervention	75	75	75	73	57	42

Error bars indicate 95% confidence intervals. A, Between-group level of significance: $P = .41$ at time 0, $P = .12$ at 3 months, $P < .001$ at 6, 9, 12, and 15 months. B, Between-group level of significance: $P = .49$ at time 0, $P = .17$ at 3 months, $P < .001$ at 6, 9, 12, and 15 months.

decreased in the intervention group (from 1.3 [95% CI, 1.1-1.5] at baseline to 1.2 [95% CI, 0.9-1.5] at 15 months, $P = .03$) and increased in the control group (from 1.4 [95% CI, 1.2-1.6] at baseline to 1.7 [95% CI, 1.4-2.0] at 15 months, $P = .02$) (eFigure 1 in Supplement), with significant effect of group allocation at 15 months ($P < .001$). Levels of serum glucose ($P < .001$), insulin ($P < .001$), CRP ($P < .001$), and total and low-density lipoprotein cholesterol ($P < .001$) decreased and of high-density lipoprotein cholesterol ($P < .001$) increased in both groups. Levels of serum triglycerides decreased only in the intervention group ($P < .001$). Levels of insulin ($P < .001$) and CRP ($P < .001$) decreased more in the intervention group than in the control group (Table 2).

Safety

Adverse events are outlined in eTable 7 in Supplement. Instability in INR was observed, with 1 patient withdrawn for a persistent INR less than 2.0 and another for an INR greater than 4. No serious bleeding was observed in either group. Postural symptoms, which frequently occurred with systolic blood pressure less than 100 mm Hg or a postural decrease greater than 10 mm Hg, resolved with reduction in use of antihypertensive agents.

Catheter Ablation Management of Atrial Fibrillation

Catheter ablation was undertaken in 14 patients in the control group (all ablation of atrial fibrillation) compared with 10 in the intervention group (9 ablation of atrial fibrillation and 1 atrioventricular-node ablation). There was no significant reduction in the need for ablation in the intervention group (odds ratio, 0.67 [95% CI, 0.28-1.6]; $P = .41$); however, this study was not designed or powered to examine the effects on need for catheter ablation. To address the effects of catheter ablation on atrial fibrillation, sensitivity analyses were performed for the primary outcomes following the exclusion of controls who underwent ablation of atrial fibrillation and indicated unchanged study findings (eTable 3 in Supplement). Given the differential timing as well as likelihood of catheter ablation in each group and that in many cases ablation likely represented treatment failure, sensitivity analyses were conducted treating catheter ablation as a treatment failure. A moderately conservative approach would be to impute return to baseline symptoms score. The least conservative approach would be to impute last measured symptom score before ablation. In the first analysis, atrial fibrillation symptom burden score, symptom severity score, episode frequency score, episode duration score, and global episode severity score, as well as atrial fibrillation cumulative duration (of all episodes on Holter recording) and the occurrence of any atrial fibrillation episode (≥30 seconds on Holter recording) were imputed as baseline values from the time of any procedure for ablation of atrial fibrillation (eFigure 7 in Supplement). This did not change the significance of the difference between the intervention and the control groups.

In the second analysis we imputed the last AFSS score prior to the ablation (eFigure 8 in Supplement). This analysis similarly did not alter the finding of a significant benefit in favor of the intervention group.

Patient Dropout and Sensitivity Analysis

Descriptive analysis of the dropout population is shown in eTable 5 and eTable 6 in Supplement. For AFSS frequency, departures of ±2 points could be tolerated and for AFSS episode severity, departures of ±1 point could be tolerated, without loss of advantage in the intervention group in these subscales. For AFSS duration, the intervention group's advantage was maintained for all departures from missing at random tested. For AFSS symptom severity subscale, departures from missing at random up to ±3 points among either the intervention or the control group could be tolerated before coefficient 95% confidence limits crossed zero and statistically significant advantage of the treatment group allocation was lost. The outcomes of this sensitivity analysis are shown in eFigure 6A-F in Supplement. For ambulatory rhythm monitoring, at all tested values of informatively missing odds ratios from 0 to 1, this result remained consistently in favor of the treatment group. Furthermore, in addition to the reduction in the number of atrial fibrillation episodes and their duration on ambulatory rhythm recording, in the intervention group there was a reduction in the proportion of patients experiencing at least 1 episode. This observation is in keeping with the results of the atrial fibrillation severity scores and unlikely to represent a skewed effect from a subgroup of the cohort. In addition, the patient's decision to undergo a catheter ablation (a study censorship criterion) was symptom driven.

Discussion

In this study, a structured weight management program for highly symptomatic patients with atrial fibrillation reduced symptom burden and severity and reduced antiarrhythmic use when compared with attempts to optimally manage risk factors alone. The beneficial effects may be attributable to decrease in left atrial area and ventricular wall thickness, thereby reducing the left atrial hypertension that is a common finding in obese patients.[22]

Epidemiologic data suggest a 4% to 5% increased risk of developing atrial fibrillation with each 1-unit BMI increment.[23,24] The greater reduction in BMI of 3.5 units in the intervention group was accompanied by improvement in other risk factors. Obesity, hypertension, impaired glucose tolerance or diabetes mellitus, and obstructive sleep apnea are closely interrelated conditions previously identified as independent risk markers for atrial fibrillation. As observed in the current and prior studies, an active intervention directed primarily at weight loss has a favorable effect on all of these conditions.

Hypertension is estimated to increase the risk of atrial fibrillation by 70% to 80%.[25] The effect of hypertension management on atrial fibrillation outcomes has been previously evaluated in different patient groups. Most, but not all,[26] studies suggest a modest preventive effect on atrial fibrillation when renin-angiotensin active agents[27] are used in the presence of structural heart disease,[28] including left ventricular hypertrophy, or following cardioversion.[29] These studies have not examined the concurrent management of comorbid conditions often seen in patients with hypertension, such as sleep apnea and alcohol consumption.[30] Furthermore, the influence of alcohol consumption on risk of atrial fibrillation was estimated by Kodama et al[31] as 8% per 10-g daily consumption increment, without a safe consumption threshold. Sparse mechanistic studies have suggested atrial conduction abnormalities with low-dose alcohol,[32] thus warranting its consideration as an independent risk factor associated with atrial fibrillation. Therefore, individually and in association, hypertension and alcohol consumption may represent modifiable risk factors imparting a substantial risk of atrial fibrillation.

Although no significant association between insulin resistance and atrial fibrillation has been defined,[33] diabetes mellitus has been shown to increase the risk of new-onset atrial fibrillation by 50%.[34] This may be the result of the effects of plasma insulin and an obesogenic diet on myocardial energetics and function.[35] Additionally, an independent association between CRP level and atrial fibrillation has been established, with a 36% increased risk with each CRP-level tertile increment.[36] In our cohort, we observed a 20.26-μIU/mL (95% CI, 16.22-24.29) (140.71 [95% CI, 112.65-168.62] pmol/L) reduction in serum insulin levels and a 1.54-mg/L (95% CI, 1.07-2.02) (14.67 [95% CI, 10.19-19.24] nmol/L) reduction in serum

CRP levels, corresponding to a 60% and 48% reduction, respectively, in the intervention group, as might be expected in response to the weight loss.

Obesity, hypertension, and obstructive sleep apnea have been independently associated with atrial dilatation, which has been demonstrated to influence initiation, maintenance, and progression of atrial fibrillation.[24,37,38] Atrial dilatation can be reversed to a variable extent with aggressive management of risk factors.[39] Importantly, a reduction in left atrial size through management of hypertension has been shown to have a favorable effect on risk of new-onset atrial fibrillation.[40] It is likely that the improvement in each of the risk factors, particularly hypertension, contributed to the observed reduction in left atrial size, similar to observations reported by Gottdiener et al.[41]

Study Limitations

Although the study did not achieve the desired sample size, the randomization of 150 participants provided at least 80% power to meet the study's primary end point. The recruitment shortfall was offset by the magnitude of weight loss and reduction in the atrial fibrillation symptom burden scores in the intervention group. The study was conducted at a single center, with a highly motivated predominantly white male (67%) population. There were a number of dropouts, but they were similar between groups, and sensitivity analysis indicates that our findings in favor of the intervention group are robust, even in the face of imbalanced participant dropout. The use of the AFSS to assess the atrial fibrillation symptom burden has the potential to underestimate the true arrhythmia burden, and periodic assessment with 7-day continuous Holter monitoring may miss episodes during the nonmonitored period. An implanted loop recorder may provide a more accurate assessment of arrhythmia burden. However, the combination of 7-day continuous ambulatory recording and a validated questionnaire may have wider clinical applicability in an ambulatory setting, combining objective and subjective parameters. Last, the weight loss program counselors could not be blinded to the patient allocation. Although we believe other clinical care providers and study coordinators were unaware of patient group allocation, this was not formally assessed.

Conclusions

Atrial fibrillation significantly affects quality of life and survival.[42] Our results suggest that weight reduction and improvement of multiple cardiometabolic risk factors benefited cardiac structure, reduced atrial fibrillation events observed on ambulatory rhythm recordings, and reduced atrial fibrillation symptom burden. The lifestyle and comprehensive metabolic risk factor management program was feasible to deliver, effective, associated with a limited risk of serious adverse events, and resulted in a substantial reduction in the symptom burden and symptom severity of atrial fibrillation.

ARTICLE INFORMATION

Author Affiliations: Centre for Heart Rhythm Disorders, University of Adelaide, and Royal Adelaide Hospital, Adelaide, Australia (Abed, Leong, Shirazi, Bahrami, Middeldorp, Lau, Brooks, Sanders); Department of Medicine, University of Adelaide, and Royal Adelaide Hospital, Adelaide, Australia (Abed, Wittert); Data Management and Analysis Centre, School of Population Health and Clinical Practice, University of Adelaide, Adelaide, Australia (Lorimer); Adelaide Institute for Sleep Health, Repatriation General Hospital, Adelaide, Adelaide, Australia (Antic); College of Medicine, Biology and Environment, Australian National University and Canberra Hospital, Canberra, Australia (Abhayaratna); Department of Cardiology, Royal Melbourne Hospital, and the Department of Medicine, University of Melbourne, Melbourne, Australia (Kalman).

Author Contributions: Drs Abed and Leong had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Wittert and Sanders contributed equally to this article.
Study concept and design: Abed, Wittert, Middeldorp, Lau, Brooks, Abhayatatna, Kalman, Sanders.
Acquisition of data: Abed, Wittert, Leong, Shirazi, Bahrami, Middeldorp, Antic, Sanders.
Analysis and interpretation of data: Abed, Wittert, Leong, Lorimer.
Drafting of the manuscript: Abed, Wittert, Leong, Sanders.
Critical revision of the manuscript for important intellectual content: Abed, Wittert, Leong, Shirazi, Bahrami, Middeldorp, Lorimer, Lau, Antic, Brooks, Abhayaratna, Kalman, Sanders.
Statistical analysis: Leong, Lorimer.
Administrative, technical, or material support: Bahrami, Shirazi and Middeldorp.
Study supervision: Abed, Wittert, Sanders.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Abed is supported by the Australian Postgraduate Award and an Earl Bakken Electrophysiology Scholarship from the University of Adelaide. Dr Leong reported being supported by a Postdoctoral Fellowship jointly funded by the National Health and Medical Research Council (NHMRC) and National Heart Foundation of Australia (NHFA). Dr Lau reported being supported by a Postdoctoral Fellowship from the NHMRC. Drs Brooks, Abhayaratna, and Sanders reported being supported by the NHFA. Dr Sanders reported being supported by a Practitioner Fellowship from the NHMRC. Dr Antic reported receiving lecture fees from RESMED and Boehringer-Ingleheim. Dr Kalman reported receiving lecture fees from Bard Electrophysiology. Dr Kalman reported receiving research support from Medtronic, St Jude Medical, and Biosense-Webster. Dr Sanders reported serving on the advisory board of Biosense-Webster, Medtronic, St Jude Medical, sanofi-aventis, and Merck Sharpe & Dohme. Dr Sanders reported receiving lecture and/or consulting fees from Biosense-Webster, Medtronic, St Jude Medical, Boston Scientific, Merck Sharpe & Dohme, Biotronik, and sanofi-aventis. Dr Sanders reported receiving research funding from Medtronic, St Jude Medical, Boston Scientific, Biotronik, and Sorin.

Funding/Support: This study was sponsored by the University of Adelaide. It was supported by funds from the Centre of Heart Rhythm Disorders at the University of Adelaide. The meal replacements were provided without cost by Prima Health Solutions Pty Ltd. Prima Health Solutions had no other involvement in the study. OBEMAN was developed by Dr Wittert with funding from Abbott Australia. The IP for the software is fully held by Dr Wittert and was used without the payment of any license fees.

Role of the Sponsor: The design, approval, and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript; and the decision to submit the manuscript for publication was executed through the employees and students (Abed, Wittert, Leong, Bahrami, Lorimer, Lau, Brooks, and Sanders) and affiliations of The University of Adelaide (Shirazi, Middeldorp, Antic, Abhayaratna, and Kalman), and overseen by it.

Additional Contributions: Paul Dorian, MD (Division of Cardiology, University of Toronto, and St Michael's Hospital), kindly provided written permission for use of the University of Toronto Atrial Fibrillation Severity Score.

Correction: This article was corrected online January 14, 2014, for a typographical error in Table 1.

REFERENCES

1. Braunwald E. Shattuck lecture—cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. *N Engl J Med*. 1997;337(19):1360-1369.

2. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications

on the projections for future prevalence. *Circulation*. 2006;114(2):119-125.

3. Coyne KS, Paramore C, Grandy S, Mercader M, Reynolds M, Zimetbaum P. Assessing the direct costs of treating nonvalvular atrial fibrillation in the United States. *Value Health*. 2006;9(5):348-356.

4. Wanahita N, Messerli FH, Bangalore S, Gami AS, Somers VK, Steinberg JS. Atrial fibrillation and obesity—results of a meta-analysis. *Am Heart J*. 2008;155(2):310-315.

5. Russo C, Jin Z, Homma S, et al. Effect of obesity and overweight on left ventricular diastolic function: a community-based study in an elderly cohort. *J Am Coll Cardiol*. 2011;57(12):1368-1374.

6. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. *JAMA*. 1999;282(22):2131-2135.

7. Karason K, Mølgaard H, Wikstrand J, Sjöström L. Heart rate variability in obesity and the effect of weight loss. *Am J Cardiol*. 1999;83(8):1242-1247.

8. Stritzke J, Markus MR, Duderstadt S, et al; MONICA/KORA Investigators. The aging process of the heart: obesity is the main risk factor for left atrial enlargement during aging the MONICA/KORA (monitoring of trends and determinations in cardiovascular disease/cooperative research in the region of Augsburg) study. *J Am Coll Cardiol*. 2009;54(21):1982-1989.

9. Nattel S, Burstein B, Dobrev D. Atrial remodeling and atrial fibrillation: mechanisms and implications. *Circ Arrhythm Electrophysiol*. 2008;1(1):62-73.

10. Wong CX, Abed HS, Molaee P, et al. Pericardial fat is associated with atrial fibrillation severity and ablation outcome. *J Am Coll Cardiol*. 2011;57(17):1745-1751.

11. Abed HS, Samuel CS, Lau DH, et al. Obesity results in progressive atrial structural and electrical remodeling: implications for atrial fibrillation. *Heart Rhythm*. 2013;10(1):90-100.

12. Sumithran P, Prendergast LA, Delbridge E, et al. Long-term persistence of hormonal adaptations to weight loss. *N Engl J Med*. 2011;365(17):1597-1604.

13. Appel LJ, Clark JM, Yeh HC, et al. Comparative effectiveness of weight-loss interventions in clinical practice. *N Engl J Med*. 2011;365(21):1959-1968.

14. Dorian P, Jung W, Newman D, et al. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. *J Am Coll Cardiol*. 2000;36(4):1303-1309.

15. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106(25):3143-3421.

16. Khoo J, Piantadosi C, Worthley S, Wittert GA. Effects of a low-energy diet on sexual function and lower urinary tract symptoms in obese men. *Int J Obes (Lond)*. 2010;34(9):1396-1403.

17. EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. *Sleep*. 1992;15(2):173-184.

18. Flemons W, Buysse D, Redline S, et al. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research: the Report of an American Academy of Sleep Medicine Task Force. *Sleep*. 1999;22(5):667-689.

19. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18(12):1440-1463.

20. Singh SN, Tang XC, Singh BN, et al; SAFE-T Investigators. Quality of life and exercise performance in patients in sinus rhythm versus persistent atrial fibrillation: a Veterans Affairs Cooperative Studies Program Substudy. *J Am Coll Cardiol*. 2006;48(4):721-730.

21. Elobeid MA, Padilla MA, McVie T, et al. Missing data in randomized clinical trials for weight loss: scope of the problem, state of the field, and performance of statistical methods. *PLoS One*. 2009;4(8):e6624.

22. Munger TM, Dong YX, Masaki M, et al. Electrophysiological and hemodynamic characteristics associated with obesity in patients with atrial fibrillation. *J Am Coll Cardiol*. 2012;60(9):851-860.

23. Tedrow UB, Conen D, Ridker PM, et al. The long- and short-term impact of elevated body mass index on the risk of new atrial fibrillation the WHS (Women's Health Study). *J Am Coll Cardiol*. 2010;55(21):2319-2327.

24. Wang TJ, Parise H, Levy D, et al. Obesity and the risk of new-onset atrial fibrillation. *JAMA*. 2004;292(20):2471-2477.

25. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol*. 1998;82(8A):2N-9N.

26. Disertori M, Latini R, Barlera S, et al; GISSI-AF Investigators. Valsartan for prevention of recurrent atrial fibrillation. *N Engl J Med*. 2009;360(16):1606-1617.

27. Wachtell K, Lehto M, Gerdts E, et al. Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: the Losartan Intervention For End Point Reduction in Hypertension (LIFE) study. *J Am Coll Cardiol*. 2005;45(5):712-719.

28. Healey JS, Baranchuk A, Crystal E, et al. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. *J Am Coll Cardiol*. 2005;45(11):1832-1839.

29. Madrid AH, Bueno MG, Rebollo JM, et al. Use of irbesartan to maintain sinus rhythm in patients with long-lasting persistent atrial fibrillation: a prospective and randomized study. *Circulation*. 2002;106(3):331-336.

30. Klatsky AL, Friedman GD, Siegelaub AB, Gérard MJ. Alcohol consumption and blood pressure Kaiser-Permanente Multiphasic Health Examination data. *N Engl J Med*. 1977;296(21):1194-1200.

31. Kodama S, Saito K, Tanaka S, et al. Alcohol consumption and risk of atrial fibrillation: a meta-analysis. *J Am Coll Cardiol*. 2011;57(4):427-436.

32. Marcus GM, Smith LM, Whiteman D, et al. Alcohol intake is significantly associated with atrial flutter in patients under 60 years of age and a shorter right atrial effective refractory period. *Pacing Clin Electrophysiol*. 2008;31(3):266-272.

33. Fontes JD, Lyass A, Massaro JM, et al. Insulin resistance and atrial fibrillation (from the Framingham Heart Study). *Am J Cardiol*. 2012;109(1):87-90.

34. Benjamin EJ, Levy D, Vaziri SM, et al. Independent risk factors for atrial fibrillation in a population-based cohort: the Framingham Heart Study. *JAMA*. 1994;271(11):840-844.

35. Wright JJ, Kim J, Buchanan J, et al. Mechanisms for increased myocardial fatty acid utilization following short-term high-fat feeding. *Cardiovasc Res*. 2009;82(2):351-360.

36. Peña JM, MacFadyen J, Glynn RJ, Ridker PM. High-sensitivity C-reactive protein, statin therapy, and risks of atrial fibrillation: an exploratory analysis of the JUPITER trial. *Eur Heart J*. 2012;33(4):531-537.

37. Tsang TS, Barnes ME, Miyasaka Y, et al. Obesity as a risk factor for the progression of paroxysmal to permanent atrial fibrillation: a longitudinal cohort study of 21 years. *Eur Heart J*. 2008;29(18):2227-2233.

38. Dimitri H, Ng M, Brooks AG, et al. Atrial remodeling in obstructive sleep apnea: implications for atrial fibrillation. *Heart Rhythm*. 2012;9(3):321-327.

39. Cocco G, Pandolfi S. Physical exercise with weight reduction lowers blood pressure and improves abnormal left ventricular relaxation in pharmacologically treated hypertensive patients. *J Clin Hypertens (Greenwich)*. 2011;13(1):23-29.

40. Wachtell K, Gerdts E, Aurigemma GP, et al. In-treatment reduced left atrial diameter during antihypertensive treatment is associated with reduced new-onset atrial fibrillation in hypertensive patients with left ventricular hypertrophy: the LIFE Study. *Blood Press*. 2010;19(3):169-175.

41. Gottdiener JS, Reda DJ, Williams DW, Materson BJ, Cushman W, Anderson RJ. Effect of single-drug therapy on reduction of left atrial size in mild to moderate hypertension: comparison of six antihypertensive agents. *Circulation*. 1998;98(2):140-148.

42. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*. 1998;98(10):946-952.