Catheter Ablation vs Lifestyle Modification With Antiarrhythmic Drugs to Treat Atrial Fibrillation

PRAGUE-25 Trial

Pavel Osmancik, MD, PhD,[a] Tomas Roubicek, MD, PhD,[b] Stepan Havranek, MD, PhD,[c] Jan Chovancik, MD, PhD,[d] Veronika Bulkova, MSc, PhD,[e] Dalibor Herman, MD, PhD,[a] Martin Matoulek, MD, PhD,[c] Vladimir Tuka, MD, PhD,[c] Ivan Ranic, MD,[d] Jana Hozmanova, MSc,[a] Marek Hozman, MD, PhD,[a] Lucie Znojilova, MSc,[a] Adam Latinak, MD,[b] Jan Pidhorodecky, MD,[b] Milan Dusik, MD, PhD,[c] Jan Simek, MD, PhD,[c] Otakar Jiravsky, MD,[d] Bogna Jiravska-Godula, MD,[d] Frantisek Lehar, MD, PhD,[e] Michal Cernosek, MD,[e] Zuzana Hejdukova, MD,[a] Hana Zelinkova, MSc,[f] Jiri Jarkovsky, PhD,[f] Klara Benesova, MSc[f]

ABSTRACT

BACKGROUND Obesity is an important risk factor for atrial fibrillation (AF). Nonrandomized studies have shown that weight loss and increased physical activity are associated with AF reduction.

OBJECTIVES The goal of this study was to assess whether treatment based on lifestyle modification (LFM; directed weight loss and physical exercise) in combination with antiarrhythmic drugs (AADs) is noninferior to catheter ablation (CA) in patients with AF and obesity.

METHODS In a randomized multicenter noninferiority trial, we enrolled patients with paroxysmal or persistent AF and a body mass index (BMI) of 30-40 kg/m^2. Patients were randomized to the CA vs LFM+AAD groups in a 1:1 ratio. Seven-day electrocardiographic Holter recordings were performed every 3 months. The primary endpoint was AF freedom during the 12 months after randomization (ie, absence of any AF episode lasting >30 s; the blanking period was 3 months). Secondary endpoints included AF burden, peak oxygen uptake during cardiopulmonary exercise testing, changes in metabolic parameters, and quality of life as assessed with the Atrial Fibrillation Effect on Quality of Life (AFEQT) questionnaire, all compared between randomization and 12 months.

RESULTS A total of 212 patients were enrolled and randomized. Nine patients withdrew consent, leaving 203 patients for the final analysis; 100 patients were allocated to the CA group and 103 to the LFM+AAD group (overall age 60 ± 9 years, 31.5% female, BMI 34.9 ± 3.0 kg/m^2, 55.7% with paroxysmal AF); the mean follow-up time was 23.5 months. The percentage of patients with AF freedom at 12 months was 73.0% (95% CI: 64.3%-81.7%) in the CA group and 34.6% (95% CI: 25.3%-43.9%) in the LFM+AAD group ($P_{\text{noninferiority}} = 0.99$, $P_{\text{superiority}} < 0.001$). Weight change (−6.4 ± 7.9 kg vs −0.35 ± 4.8 kg; $P < 0.001$) and decreased HbA_{1c}, were more significant in the LFM+AAD group than in the CA group.

CONCLUSIONS Despite important metabolic improvements associated with LFM, CA was superior to LFM combined with AADs in improving freedom from AF at 1 year in patients with AF and obesity. (JACC. 2025;86:18-28)

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From the [a]Cardiocenter, Third Faculty of Medicine, Charles University Prague and University Hospital Kralovske Vinohrady, Prague, Czech Republic; [b]Department of Cardiology, Regional Hospital, Liberec, Czech Republic; [c]Cardiocenter, Second Internal Clinic—Cardiology and Angiology, Charles University, General Faculty Hospital, Prague, Czech Republic; [d]Department of Cardiology, Cardiocenter, Hospital Podlesí, Trinec, Czech Republic; [e]Department of Cardiology, Neuron Medical Center, Hospital Brno, Brno, Czech Republic; and the [f]Institute of Biostatistics and Analyses, Faculty of Medicine, Masaryk University, Masaryk, Czech Republic.

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Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and affects an estimated 60 million people worldwide.[1] Epidemiologic studies have demonstrated that obesity is one of the strongest predictors of developing AF.[2] An interindividual difference in body mass index (BMI) of 5 kg/m^2 is associated with a 19% to 29% higher incidence of AF.[3]

Catheter ablation (CA) has been documented as the most effective treatment of AF. CABANA (Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial) (the largest randomized controlled trial [RCT] that compared CA and antiarrhythmic drugs [AADs] for AF treatment) reported that 36.4% of ablation patients and 59.2% of drug-therapy patients had experienced a recurrence of AF within 12 months.[4]

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Obesity was very prevalent among patients in RCTs that assessed the effect of CA. The median BMI in the CABANA trial was 30 kg/m^2.[5] A median BMI of 30 kg/m^2 was reported in the EARLY-AF trial, which compared cryoablation with AADs,[6] and a mean BMI of 28.5 kg/m^2 was reported in the ADVENT (Pulsed Field or Conventional Thermal Ablation for Paroxysmal Atrial Fibrillation) trial, which compared thermal with pulsed-field ablation.[7] In AF patients with BMI ≥27, directed weight loss and other lifestyle modifications (LFMs), it has been shown that including increasing physical activity, have been associated with improved SR maintenance.[8] In the nonrandomized LEGACY (Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study), weight losses >10% and 3% to 9% of body weight resulted in AF freedom without AADs or CA in 45.5% and 22.2% of patients, respectively.[8] However, in trials comparing CA with medical treatment, no weight reduction or other LFM programs were part of the medical arms, even though almost one-half of the studied population had a BMI ≥30 kg/m^2. Based on the positive results of LFM on sinus rhythm (SR) maintenance, we hypothesized that LFM can significantly augment the treatment effects of AADs in obese AF patients. Therefore, we initiated an RCT with the main question of whether the combination of LFM+AAD can serve as a noninferior alternative to CA in AF patients with obesity.

METHODS

TRIAL DESIGN. The PRAGUE-25 (Catheter Ablation vs. AADs and Risk Factor Modification; NCT04011800) trial is a randomized, multicenter, investigator-initiated, noninferiority trial. The trial was conducted in 5 centers in the Czech Republic (listed in the Supplemental Appendix). The study was approved by the Ethics Committee at the University Hospital Kralovske Vinohrady (EK-VP/34/0/2020) and the ethics committees of all participating centers. All patients signed informed consents before enrollment. The details of the protocol were published previously[9] and are provided in the Supplemental Material. Data collection and analyses were performed by the Institute for Biostatistical Analyses (Masaryk University, Brno, Czech Republic) and Charles University (Prague, Czech Republic). The first author prepared the article, and all authors have confirmed the accuracy of the data and approved the article. The trial was supported by a peer-reviewed research grant from the Czech Health Research Council, Czech Republic: NU21-02-00388.

PATIENT POPULATION AND RANDOMIZATION. Patients with symptomatic AF who met all of the following criteria were eligible: symptomatic AF (paroxysmal, persistent, or long-standing persistent). BMI 30-40 kg/m^2, and signed informed consent.

The most important exclusion criteria were a history of tachycardia-induced cardiomyopathy, BMI >40 kg/m^2, left ventricular ejection fraction ≤40%, untreated coronary artery disease, left atrial size >60 mm, indication for surgical treatment of obesity, age ≥75 years, contraindication for AADs, and significant limitations that could affect physical activity. Further inclusion and exclusion criteria are detailed in the Supplemental Appendix. At the baseline visit, all patients in both groups were informed, in detail, about the risk of obesity as well as other risk factors as they related to AF. Eligible patients meeting the inclusion criteria were randomized in a 1:1 ratio to the catheter ablation (CA) group or the LFM plus AADs (LFM+AAD) group. Randomization was done using a Web-based system in permuted blocks, with stratification according to BMI, sex, and AF type.

BASELINE EXAMINATIONS. After randomization, all patients underwent: 1) a baseline cardiopulmonary exercise test (CPET) (Supplemental Appendix); 2) echocardiography; 3) quality of life analysis (using the Atrial Fibrillation Effect on Quality of Life questionnaire [AFEQT]); 4) blood biochemistry; and 5) a baseline 7-day electrocardiographic (ECG) Holter recording. All baseline examinations were done within 4 weeks of randomization.

ABBREVIATIONS AND ACRONYMS

AAD = antiarrhythmic drug
AF = atrial fibrillation
BMI = body mass index
CA = catheter ablation
CPET = cardiopulmonary exercise test
ECG = electrocardiography
GLP-1 = glucagon-like peptide 1
ITT = intention-to-treat
LFM = lifestyle modification
PP = per-protocol
RCT = randomized controlled trial
SCD = sudden cardiac death
SR = sinus rhythm

TRIAL PROCEDURES. CA group. Patients in the CA group underwent an CA procedure within 6 weeks of randomization. The CA protocol is described in the Supplemental Appendix. The first 3 months after CA were considered to be the blanking period. AADs or cardioversions were allowed in the CA group only during the blanking period; all AADs had to be stopped before the end of the 3-month blanking period. The reinitiation of AADs after the blanking period was allowed only in cases of arrhythmia recurrence and was considered to be treatment failure.

LFM + AAD group. The full LFM+AAD program was started within 4 weeks after randomization. LFM was not managed by treating cardiologists, but by teams of dietary specialists and physiotherapists. The initial patient consultations with nutritional specialists and physiotherapists occurred during the 4 weeks after randomization. In addition to regular in-person and telephone consultations, patients were encouraged to record their calorie intake and exercise activity with the use of the OBEFIS mobile phone application. Besides reducing calorie intake, patients were instructed and repeatedly encouraged to decrease alcohol consumption (but complete abstinence was not required). All patients had a consultation with a physiotherapist, who prepared individual exercise programs based on the CPET results. Patients monitored their heart rate during exercise with the use of a fitness band. Details regarding LFM are provided in the Supplemental Appendix. The initiation of antiarrhythmic medication in LFM+AAD patients commenced within 4 weeks of randomization, with the dosage up-titration during the first 3 months after randomization. The choice of AAD for each patient was determined according to local practice; amiodarone was available as a third-line choice only after previous failure of class IC AADs, and, in contrast to the CA group, the use of AADs was allowed during the whole follow-up. Similarly, as in the CA patients, the first 3 months after the start of the LFM program were considered to be the blanking period. Blood pressure, lipids, and diabetes were managed similarly in both groups by the study's cardiologists or the patients' diabetologists according to current guidelines.

OUTPATIENT FOLLOW-UP AND HOLTER MONITORING. Starting from the day of CA or the start of the full LFM+AAD program (ie, day 0 [D0]), follow-up visits were performed at 3, 6, 9, and 12 months and then every 6 months. At the 3-month follow-up visit, all patients in AF (ie, both groups) underwent electrical cardioversion. In the first 3 months after D0, which were considered to be the blanking period in both groups, AF recurrences were not considered as an endpoint.

Seven-day Holter recordings were performed every 3 months during the first year and every 6 months thereafter. Evaluations of Holter recordings were blinded; all Holter recordings were evaluated by an organization outside of the study without access to patient information (Medical Data Transfer).

Starting from D0, outpatient visits were also performed every 3 months in the first year and every 6 months thereafter. During each outpatient visit, all new urgent or unscheduled visits due to AF or other cardiovascular reasons, other important changes in the health status, and all changes in medication, with a special focus on antiarrhythmic medication, were recorded. During the 12-month follow-up, echocardiography, quality of life evaluation, biochemistry, and CPET were repeated.

TRIAL ENDPOINTS. The primary endpoint (AF freedom) was the absence of any atrial tachyarrhythmia (AF, atrial flutter, or atrial tachycardia) lasting >30 seconds during the 1 year following the blanking period. Evaluation of arrhythmia recurrence was conducted with the use of 7-day Holter recording analyses, ECGs conducted during outpatient visits, and, if applicable, documented AF at unplanned patient visits (patient-reported palpitation without documented AF was not considered to be an AF recurrence).

The secondary endpoints were changes in AF burden (expressed as a percentage of time in AF during Holter recording), peak VO_2 max during CPET, AFEQT scores, and prespecified metabolic parameters (body weight, lipid levels, and glycated hemoglobin [HbA_{1c}] levels) between baseline and the 12-month visit.

STATISTICAL CONSIDERATIONS AND POWER CALCULATION. In a meta-analysis of 24 RCTs comparing CA, AADs, and placebo, the overall success rate of AADs, defined as the disappearance of arrhythmia during follow-up, was 52% (95% CI: 47%-57%).[10] In the CABANA and STOP-AF (Cryoballoon Catheter Ablation in Antiarrhythmic Drug Naive Paroxysmal Atrial Fibrillation) trials, the 1-year AF freedoms in the medication (AAD) groups were 47.1%, and 45.0%, respectively.[5,11] Several nonrandomized studies documented the positive effect of LFM on AF freedom. In the LEGACY study, 45.5% of patients who achieved >10% weight loss and 22.2% of patients who achieved 3% to 9% weight loss remained AF free without AADs or ablation. Therefore, an additional effect of 20% was expected for weight loss and physical exercise; we assumed an absence of any

atrial tachyarrhythmia in 65% of patients in the LFM+AAD group at 12 months after randomization.

Concerning the efficacy of CA, AF freedom was present in 63.6% at 12 months in the CABANA trial.[5] In a meta-analysis of RCTs comparing CAs to AADs, the single-procedure success rate of CA without AADs was 57% (95% CI: 50%-64%).[10] The median BMI in most published studies on CA for AF was ~30 kg/m^2. Because the minimum BMI in our study was 30 kg/m^2, and because the effect of CA decreases with increased BMI, the expected 1-year AF freedom in the CA group in our study was 60%.

The first step in selecting the noninferiority margin was to estimate the minimum acceptable retention of CA over placebo. No studies comparing CA and AADs had a placebo arm. In studies comparing AADs and placebo, the overall success rate (generally defined as the disappearance of arrhythmia during follow-up) in 8 placebo treatment arms was 24.9% (95% CI: 15%-34%).[10] A noninferiority margin of 12% was selected, which was less than the lower band of the 95% CI, or one-half of the treatment effect of placebo. If expressed as an OR, it corresponds to 1.65, which is less than the most liberal margin of 1.92 required by regulatory guidelines. Details on the statistical considerations of treatment effect and power calculation are described in the Supplemental Appendix. The sample size for the noninferiority analysis was estimated with the use of a 1-sided z-test. The sample size calculation assumed 80% power, 2.5% 1-sided alpha, and a noninferiority margin of 12%. Using these assumptions, 202 patients (101 in each group) would need to be enrolled to demonstrate noninferiority. With an expected drop-out rate of 5%, 212 patients were initially planned. Because the analysis of the primary endpoint was planned for 1 year after randomization, all patients had to have at least 1 year of follow-up after randomization.

TABLE 1 Baseline Characteristics

	CA Group (n = 100)	LFM+AAD Group (n = 103)
Age, y	60 ± 8	60 ± 9
Male	68 (68.0)	71 (68.9)
Body weight, kg	110 ± 15	109 ± 17
Body mass index, kg/m^2		
Mean	35.0 ± 2.9	34.9 ± 3.2
30.0-32.9	30 (30.0)	35 (34.0)
33.0-35.9	33 (33.0)	30 (29.1)
≥36.0	37 (37.0)	38 (36.9)
AF type		
Paroxysmal	56 (56.0)	57 (55.3)
Persistent	39 (39.0)	41 (39.8)
Long-standing persistent	5 (5.0)	5 (4.9)
Medical history		
Heart failure	13 (13.0)	11 (10.7)
Hypertension	84 (84.0)	86 (83.5)
Diabetes mellitus	19 (19.0)	30 (29.1)
Stroke/TIA	3 (3.0)	3 (2.9)
Coronary artery disease	8 (8.0)	6 (5.8)
History of myocardial infarction	3 (3.0)	1 (1.0)
CHA_2DS_2-VASc score		
Mean	2.0 ± 1.2	2.0 ± 1.2
0	7 (7.0)	9 (8.7)
1	33 (33.0)	29 (28.2)
2	27 (27.0)	30 (29.1)
3	20 (20.0)	21 (20.4)
>3	12 (12)	14 (13.6)
History of electrical cardioversion	36 (36.0)	47 (45.6)
Pacemaker	3 (3.0)	1 (1.0)
Baseline medication		
AADs	59 (59.0)	69 (67.0)
Oral anticoagulants	90 (90.0)	92 (89.3)
BBs	75 (75.0)	86 (83.5)
No. of antihypertensives including BBs	2.3 ± 1.3	2.3 ± 1.2
Statins	50 (50.0)	51 (49.5)
Fibrates	5 (5.0)	5 (4.9)
Ezetimib	4 (4.0)	2 (1.9)
Antidiabetics	18 (18.0)	27 (26.2)
Echocardiography		
Left atrium diameter, mm	45.0 ± 6.2	45.6 ± 5.7
LVEF, %	59.2 ± 8.3	61.2 ± 5.6

Values are shown as n (%) or mean ± SD. *P* values were calculated with the use of Fisher test or Mann-Whitney *U*-test.

ADD = antiarrhythmic drug; BB = beta-blocker; CA = catheter ablation; LFM = lifestyle modification; LVEF = left ventricular ejection fraction; TIA = transient ischemic attack.

STATISTICAL ANALYSIS. Analyses of the primary and secondary endpoints were based on the intention-to-treat (ITT) and per-protocol (PP) principles. If the noninferiority criterion for the primary endpoint was not satisfied, then superiority was evaluated. Standard descriptive statistical methods were used in the analysis. Categoric data were summarized with the use of absolute and relative frequencies, whereas continuous data were described with the use of either mean ± SD or median (Q1-Q3), depending on data distribution. Kaplan-Meier estimations and Cox proportional hazards regression models were used for data visualization and analysis, with the treatment group included as a covariate. The noninferiority of LFM+AAD was assessed with the use of a 1-sided z-test based on differences in 12-month AF-free survival proportions, with a noninferiority margin of 12%. Subsequently, the superiority of CA was evaluated with the use of a 1-sided z-test. Secondary endpoints were evaluated by means of the Mann-Whitney test to assess the statistical significance of differences between the 2 groups. In

TABLE 2 Weight Change (kg) During Follow-Up

	n	CA	n	LFM+AAD	Mean Difference (95% CI)	*P* Value
Baseline visit	100	109.5 ± 14.6	103	109.3 ± 17.2	0.27 (−4.15 to 4.68)	0.581
3-month visit	100	109.2 ± 14.5	102	106.2 ± 18.2	3.00 (−1.57 to 7.56)	0.073
6-month visit	100	109.1 ± 14.4	100	104.5 ± 18.9	4.60 (−0.08 to 9.28)	0.016[a]
9-month visit	100	109.4 ± 15.2	100	103.3 ± 18.6	6.14 (1.41-10.87)	0.004[a]
12-month visit	100	109.2 ± 15.5	100	103.1 ± 19.0	6.11 (1.26-10.95)	0.004[a]
18-month visit	70	108.1 ± 14.9	73	102.5 ± 18.0	5.60 (0.15-11.06)	0.016[a]
24-month visit	46	108.3 ± 13.9	57	101.0 ± 19.2	7.27 (0.81-13.74)	0.008[a]

Values are mean ± SD unless otherwise indicated. [a]$P < 0.05$.
Abbreviations as in Table 1.

addition, the paired Wilcoxon signed rank test was used to evaluate the statistical significance of changes within each group between baseline and 12-month values.

Because the planned statistical analyses did not include adjustments for multiplicity when evaluating secondary endpoints or subgroups, the results are presented as point estimates with 95% CIs. The widths of the CIs have not been adjusted for multiplicity and should not be used to infer definitive treatment effects. All statistical analyses were performed with the use of SPSS software version 29.0.1.0 and R version 4.2.2.

RESULTS

PATIENTS AND FOLLOW-UP. From May 2021 to November 2023, 212 patients were randomized (CONSORT diagram in Supplemental Figure 1). Nine patients withdrew consent within the first month after randomization, so 203 patients (60 ± 9 years of age, 31.5% female, BMI 34.9 ± 3.0 kg/m^2, and 55.7% with paroxysmal AF) entered the study and were analyzed. One hundred were randomized to the CA group and 103 to the LFM+AAD group. The baseline characteristics were balanced between the 2 groups (**Table 1**, Supplemental Table 1). During the study course, 26 patients underwent cross-over (1 from CA to LFM+AAD and 25 from LFM+AAD to CA), but only 3 (1 CA and 2 LFM+AAD) crossovers occurred before the primary endpoint had been reached. Details are shown on the study flow chart provided in Supplemental Figure 1. The mean follow-ups were 23.3 ± 8.5 months in the CA group and 23.6 ± 9.2 months in the LFM+AAD group. Adherence to Holter monitoring and CPET examinations are presented in Supplemental Table 2.

TREATMENT CHARACTERISTICS. In the CA group, 48 patients underwent radiofrequency and 51 pulsed-field ablations within 6 weeks of randomization. All patients underwent pulmonary vein isolation, and 35 patients (35.4%) with nonparoxysmal AF received additional ablation lesions. Further information about the ablations is provided in Supplemental Table 3. During follow-up, 7 patients (7%) underwent a redo ablation (and 1 patient had 2 redo ablations) because of arrhythmia recurrence. At the 12-month visit, 16 CA patients (16%) were on AADs because of documented AF recurrences (**Table 2**). Compared with baseline values, nonsignificant body weight reduction was present in CA patients at 12 months (−0.35 ± 7.78 kg) and at 24 months (−0.08 ± 5.96 kg) (**Table 2**).

In the LFM+AAD group, there was a significant reduction in body weight at 12 months compared with baseline (−6.37 ± 7.94 kg; $P < 0.001$), and that weight loss was maintained through the 24-month follow-up (−6.29 ± 8.80 kg; $P < 0.001$) (**Table 2**, Supplemental Table 4). Liraglutide or semaglutide was briefly (6 ± 4 months) used by 15 patients (14.6%). At 3 months, AADs were used in 97 LFM+AAD patients (95.1%); most patients were on propafenone or flecainide. The use of AADs over time is presented in **Table 3**. Owing to palpitations, 2 LFM+AAD patients underwent ablation before any documented occurrence of AF. Based on the questionnaire administered during the last study visit in the LFM+AAD group, 66 patients (64.1%) reported decreased alcohol consumption, 79 (76.7%) reported an increase in physical activity, and 17 (16.5%) were being treated for obstructive sleep apnea (Supplemental Table 5). Sixty-eight patients (66%) regularly used the OBEFIS mobile app to monitor their physical activity and to communicate with a dietary specialist. Details on laboratory values and medications in patients with diabetes in both groups at the 12-month visit are presented in Supplemental Tables 6 and 7.

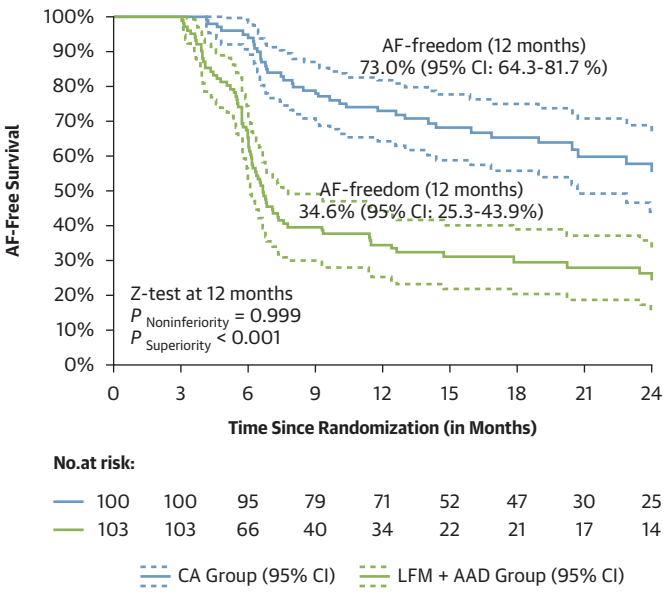
PRIMARY OUTCOME. In the ITT analysis, arrhythmia-free survival at 12 months was present in 73.0% (95% CI: 64.3%-81.7%) of patients in the CA group and 34.6% (95% CI: 25.3%-43.9%) of patients in the

TABLE 3 Proportion of Patients Using Antiarrhythmic Drugs During Follow-Up

	n	CA	n	LFM+AAD
3-month visit	100	3 (3.0)	102	97 (95.1)
Propafenone		0		46 (47.4)
Dose, mg/d		-		404 ± 134
Flecainide		0		26 (26.8)
Dose, mg/d		-		148 ± 61
Sotalol		3 (100.0)		3 (3.1)
Dose, mg/d		107 ± 46		187 ± 122
Amiodarone		0		22 (22.7)
Dose, mg/d		-		186 ± 32
6-month visit	100	10 (10.0)	100	88 (88.0)
9-month visit	100	14 (14.0)	100	77 (77.0)
12-month visit	100	16 (16.0)	100	66 (66.0)
18-month visit	70	15 (21.4)	73	47 (64.4)
24-month visit	46	7 (15.2)	57	37 (64.9)

Values are n (%) or mean ± SD.
Abbreviations as in Table 1.

FIGURE 1 Estimates of the Primary Endpoint



Shown are Kaplan-Meier estimates and 95% CIs of the primary endpoint (freedom from recurrence of any episode of atrial fibrillation [AF], atrial flutter, or atrial tachycardia lasting >30 seconds) after the blanking period after catheter ablation (CA) or onset of lifestyle modification program combined with antiarrhythmic drugs (LFM+AAD). The comparison of AF freedom at 12 months between groups was done with the *z*-test.

LFM+AAD group (**Figure 1**, Supplemental Table 8). The criteria for noninferiority of LFM+AAD to CA were not met (P for noninferiority = 0.999; [z-test]). In the subsequent superiority analysis, CA was superior to LFM+AAD ($P < 0.001$ for superiority at 12 months). The results were similar in the PP analysis (Supplemental Table 8), and the effect was similar among subgroups in post hoc analysis (**Figure 2**). The corresponding HR for AF freedom in the sensitivity analysis for the entire follow-up was 2.79 (95% CI: 1.91-4.07) (**Central Illustration**), and again, the results were similar in the PP analysis (Supplemental Figure 2).

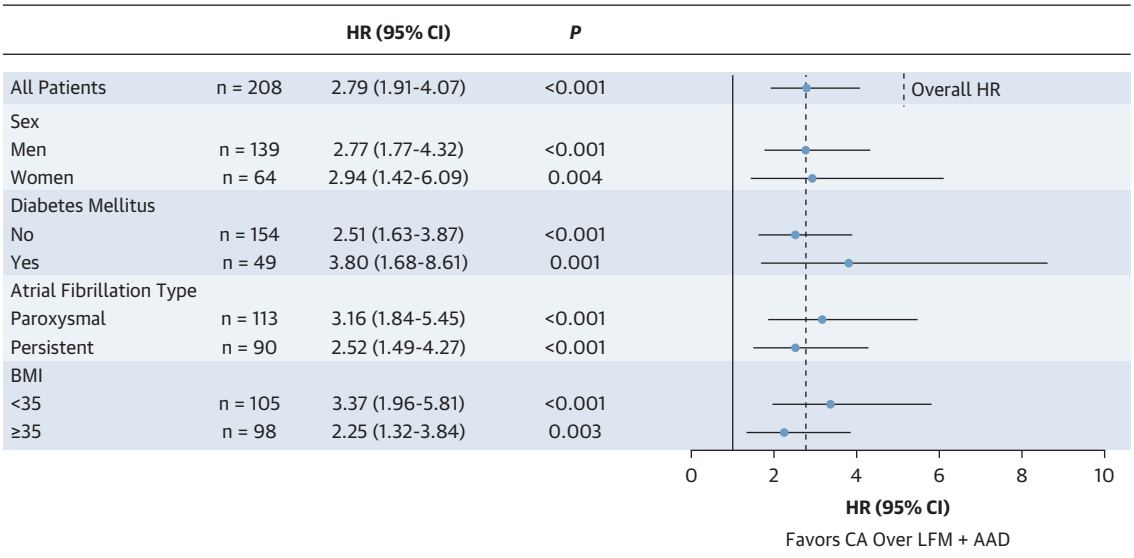
SECONDARY OUTCOMES. **Table 4** presents a summary of the secondary endpoint results from the ITT analysis. The AF burden at 12 months significantly decreased in both groups (**Table 4**, Supplemental Figure 4). Compared with baseline values, peak VO_2 increased significantly in the LFM+AAD group (+1.14 ± 3.90 mL/min per kg; $P = 0.028$) and remained unchanged in the CA group, but the between-group difference did not reach statistical significance (**Table 4**). Concentrations of N-terminal pro-B-type natriuretic peptide significantly decreased in both groups compared with baseline values, with no differences in the between-group comparisons. Compared with baseline, HbA_{1c} concentrations significantly decreased in the LFM+AAD group (−1.4 ± 4.8 mmol/L) and increased in the CA group (+2.5 ± 10.5 mmol/L) resulting in significant between-group difference at 12 months. In terms of quality of life, both groups reported similar improvements as assessed by the AFEQT (Supplemental Figure 5, **Table 4**), with no between-group differences at 12 months.

COMPLICATIONS. Clinically relevant major complications, assessed by the clinical endpoint committee, occurred in 1 CA patient (1%) and 4 LFM+AAD patients (3.8%) (Supplemental Tables 3 and 9). One CA patient had a transitory ischemic attack during the procedure. In the LFM+AAD group, 3 patients experienced syncope, and 1 patient died suddenly and without explanation. Because the autopsy finding was negative for structural heart disease, the cause was classified as sudden cardiac death (SCD). Other nonmajor complications were seen in 1 CA patient (1%) and 3 LFM+AAD patients (2.9%). A list of complications and a complete description of all adverse events are provided in Supplemental Tables 3 and 9.

DISCUSSION

In this study, we found that the treatment strategy for AF patients with obesity based on AADs and lifestyle modifications, including weight loss and increased physical exercise, was inferior to CA in terms of SR maintenance at 1 year.

FIGURE 2 **Primary Endpoint Post Hoc Subgroup Analysis (Intention to Treat)**



The circles represent the HRs, and the bars indicate the 95% CIs. BMI = body mass index.

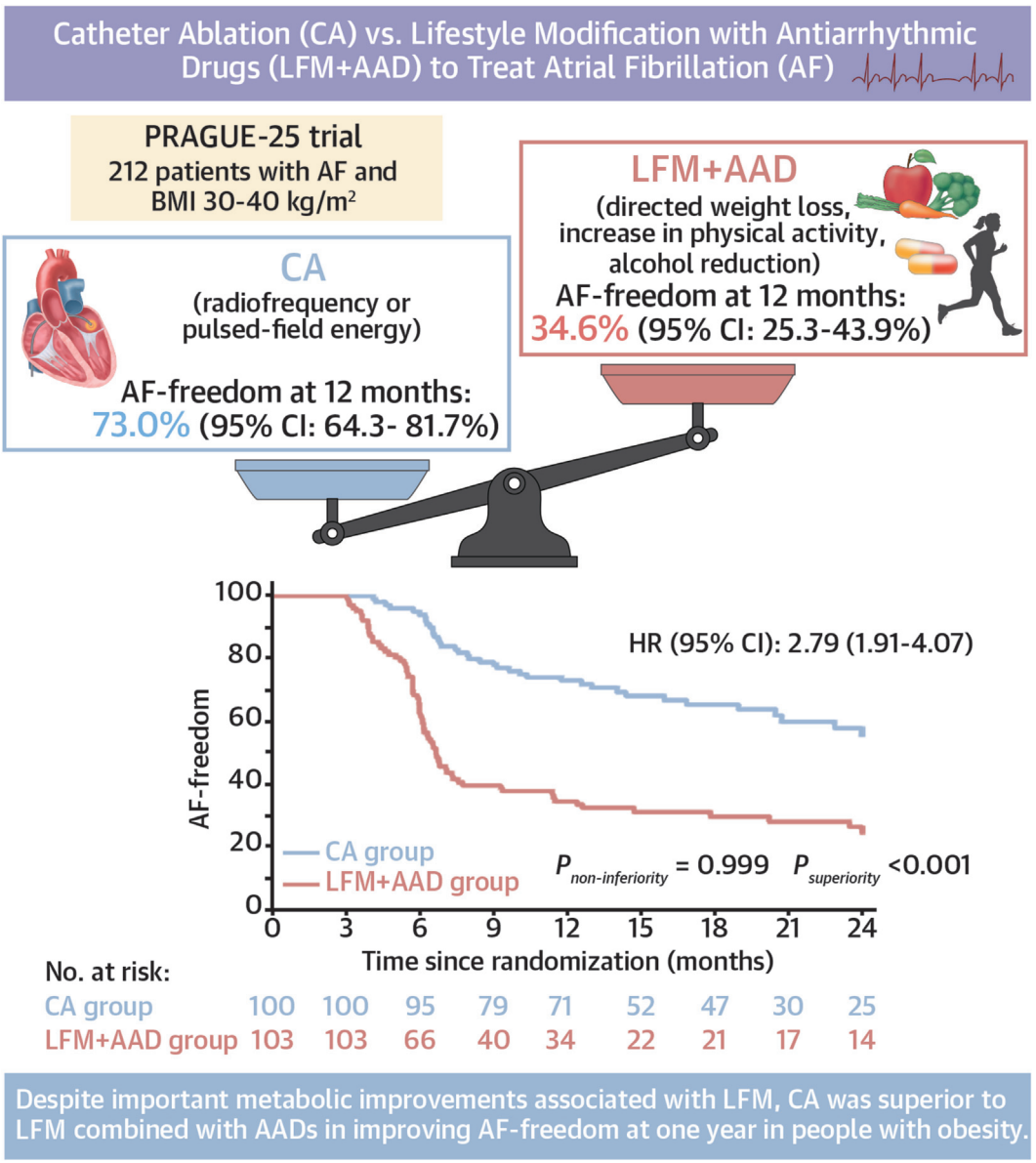
The positive effect of weight loss on AF was previously shown in the LEGACY study, which was a nonrandomized cohort study that offered directed weight loss and lifestyle modification to a cohort of 355 AF patients with BMI ≥27 kg/m^2. Weight losses of ≥10%, 3% to 9%, and ≤3% were achieved in about one-third of patients each. At the final follow-up visit, AF freedom without AADs or ablation was present in 45.5%, 22.2%, and 13.4%, respectively, and with AADs or ablation in 86.2%, 65.5%, and 36.9%, respectively, when assessed according to the patient's achieved weight loss group.[8] A very positive benefit for LFM was also present in patients after CA in the ARREST-AF (Aggressive Risk Factor Reduction Study for Atrial Fibrillation and Implications for the Outcome of Ablation) study.[12] In a design similar to the LEGACY trial, AF freedom was higher in 61 patients who accepted the LFM program vs the 88 who declined (32.9% vs 9.7% of patients).

The average weight loss in our LFM+AAD patients at 12 months was 6.37 kg, which is similar to the middle group of the LEGACY study (−6.0 kg). However, the LEGACY and ARREST-AF studies were nonrandomized, and in the ARREST-AF study, patients were divided according to their acceptance of the LFM program; patients who declined formed the control group. The absence of randomization could have significantly biased their results because motivated patients who accepted the LFM program could differ significantly in areas (well-being, drug adherence, etc) other than weight loss.

The results of the ARREST-AF study were challenged by the recent SORT-AF (SORT - AF Supervised Obesity Reduction Trial for AF Ablation Patients) trial. That trial randomized 133 AF patients with BMIs of 30 to 40 kg/m^2 after CA to either a weight-reduction program or standard care. AF burden after ablation decreased significantly in both groups, but there was no significant difference in AF burden between the weight loss and control groups 12 months after the CA.[13] It is noteworthy that compared with the ARREST-AF study, weight loss in the SORT-AF study was only modest (−4.6 ± 8.6 kg, or 3.91% of the initial body weight).[13]

The weight loss achieved in our LFM+AAD patients was modest as well. Greater weight reduction would definitely be expected if glucagon-like peptide 1 (GLP-1) agonists had been used. In meta-analyses of studies with liraglutide, semaglutide, and tirzepatide, the resulting weight loss was −4.5 kg with >1.8 mg liraglutide, −9.9 kg with >2.4 mg semaglutide, and −15.3% of the initial body weight with tirzepatide.[14,15] Unfortunately, our LFM+AAD group did not reach the planned weight loss of 10% of body weight, which is an important study limitation. Greater weight loss would most likely have led to better outcomes regarding SR maintenance. On the other hand, the weight loss achieved at 12 months was

CENTRAL ILLUSTRATION Summary of the Results



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maintained at 24 months in our study, which is in contrast to GLP-1 studies, in which treatment-related weight loss was not maintained after GLP-1 was stopped. Moreover, with regard to previous studies with GLP-1 agonists, despite the clear and significant effect on body weight, no significant effect on AF was seen in the meta-analysis of 7 RCTs that assessed the use of GLP-1 agonists on the incidence of AF (OR: 0.81; 95% CI: 0.78-1.15).[16]

In our study, 1-year AF freedom in the LFM+AAD group (34.6%) was lower than expected. In the CABANA trial, AF freedom was 40.8% in patients on AADs at 12 months.[4] In the 2 most recent RCTs on CA, AF freedom on AADs at 12 months was present in 45% (STOP-AF trial) and 32.2% (EARLY-AF trial).[6,11] Recently, Ornelas-Lorendo et al compared the effectiveness of Class 1C and III AADs in obese (BMI ≥30 kg/m²) and nonobese AF patients. Nonresponse to Class 1C AADs in patients with obesity was significantly higher than those without obesity.[17] Explanations for the lower-than-expected AF freedom in our study may be related to the lower

TABLE 4 Secondary Endpoints: AF Burden, VO_2 max, Metabolic Parameters, and AFEQT at Baseline and 12 Months

	CA Group		LFM-AAD Group		Between-Group Differences (95% CI)	P Value
	Baseline	12 Months	Baseline	12 Months		
AF burden, %	31.1 ± 42.6	12.1 ± 31.2[a]	35.9 ± 44.1	22.1 ± 37.2[b]	−4.8 (−17.3 to 7.7)	0.17
VO2 max, mL/kg/min	17.90 ± 4.57	18.05 ± 4.74	19.09 ± 5.07	20.38 ± 5.81[c]	−0.98 (−2.02 to 0.07)	0.13
HbA1c, mmol/L	39.6 ± 9.8	41.6 ± 11.2[d]	40.7 ± 7.1	39.6 ± 8.0[e]	3.9 (1.4-6.3)	<0.001[f]
Total cholesterol, mmol/L	4.52 ± 1.12	4.28 ± 0.96	4.46 ± 1.13	4.29 ± 1.10	−0.05 (−0.32 to 0.22)	0.79
Triglycerides, mmol/L	1.86 ± 1.20	1.71 ± 1.29	1.79 ± 0.87	1.50 ± 0.73[e]	0.15 (−0.11 to 0.41)	0.08
CRP, mmol/L	4.59 ± 4.82	3.77 ± 4.31	4.34 ± 4.18	3.67 ± 3.87[b]	−0.12 (−1.50 to 1.25)	0.40
NT-pro BNP, pg/mL	506 ± 566	284 ± 463[a]	495 ± 548	342 ± 412[b]	−64 (−222 to 94)	0.21
AFEQT	68.6 ± 19.9	86.2 ± 14.3[a]	72.7 ± 19.0	85.4 ± 15.4[e]	4.3 (−0.8 to 9.4)	0.14

[a]$P < 0.001$. [b]$P < 0.01$. [c]$P < 0.05$. [d]$P < 0.05$. [e]$P < 0.001$. [f]$P < 0.05$.
AFEQT = Atrial Fibrillation Effect on Quality-of-life Questionnaire.

effectiveness of Class 1C AADs (used in 74% of our patients) combined with the less-than-expected (moderate) weight reduction in our patients. Finally, the presence of manifest AF may indicate a more advanced stage of the disease, which may limit the treatment efficacy of preventive programs.

With regard to the efficacy of CA in our study, despite the higher BMIs of our patients, the 1-year AF freedom (73.0%) in our CA patients was similar to the 1-year AF freedom after CA reported in other recent trials, such as CABANA (63.6%), STOP-AF (74.6%), and ADVENT (72%).[4,7,11]

The low rate of complications in our study (1 transient ischemic attack [1%]) highlights the steadily increasing safety profile of CA. In a large series of >153,000 patients, obesity was associated with a significant risk of vascular access complications, but with only a nonsignificant trend toward other ablation-related complications.[18] The risk of vascular access complications can be reduced by periprocedural ultrasound guidance,[19] which was used on all patients in the present study. Similarly low rates of complications during CA in overweight and obese patients were also seen in the recent SORT-AF trial (0.75% of patients).[13]

In contrast, major drug-related adverse events (AEs) were present in 4 patients on AADs (3.8%). The rates of complications in previous studies comparing CA and AADs were similar. Still, the types of major AEs differed between groups,[20,21] and AEs associated with AADs were usually less clinically relevant. Our study included 1 sudden unexplained death that occurred in the LFM+AAD group in a patient being treated with propafenone. It is well established that AF is associated with increased general mortality, including SCD.[22] The use of AADs has been known for some time to be associated with a higher risk of SCD, although the risk is highest in patients with heart failure or coronary artery disease (CAD).[23] Although both of these conditions were exclusion criteria in our study, unrecognized CAD or latent channelopathy can be present in apparent healthy AF patients. Moreover, the risk of SCD in AF patients on Class 1C AADs is higher even in the absence of CAD and was described decades ago.[24] AADs are still commonly used to treat symptomatic AF; however, the risk associated with AADs should be considered before treatment onset.

The LFM+AAD group nonetheless experienced a significant decrease in body weight, an improvement in metabolic parameters, and an improvement in physical performance during CPET. At 12 months, LFM-AAD patients experienced a significant decrease in HbA_{1c} concentrations and body weight compared with CA patients. In the long term, higher HbA_{1c} concentrations are associated with increased risk of cardiovascular events and cardiovascular mortality,[25] as well as an increased risk of AF.[26] Increased body weight is associated with a higher risk of heart failure, cardiovascular events, and all-cause mortality.[27,28] Weight reduction is associated with improved outcomes, especially if cardiorespiratory fitness was part of the weight reduction program.[29] Given the strong association between these positive metabolic changes and enhanced cardiovascular outcomes, the reduced effectiveness of the LFM+AAD strategy relative to AF freedom should not dissuade obese patients from pursuing weight loss and LFM.

Compared with baseline values, the LFM program was associated with an increase in peak VO_2 at 12 months. An inverse association between decreased cardiorespiratory fitness and cardiovascular events over the long term has been described previously.[30] As was shown, significant improvements in cardiovascular outcomes occur even with small changes in peak VO_2.[29] Despite lower AF freedom in the

LFM+AAD group, the quality of life improvements were similar in both arms, which emphasizes the positive subjective perception of weight loss and, probably, the increase in physical capacity. Although the main goal of the study was to compare AF freedom at 1 year, the results should be viewed and interpreted in the context of the aforementioned improvements in the LFM+AAD group, and the positive metabolic changes in the LFM+AAD group should not be underestimated.

STUDY LIMITATIONS. GLP-1 agonists were not systematically used in the LFM+AAD group. The planned target of a 10% reduction in body weight was not achieved. Because the effect of weight loss on AF freedom in nonrandomized studies was related to achieved weight loss, greater weight loss in our patients would probably have been associated with better SR maintenance. Furthermore, the positive effect of weight loss on AF could appear later on, ie, the effect might not have been fully present during the follow-up of our study. Arrhythmia recurrences were monitored by means of 7-day ECG Holter recordings; implantable loop recorders were not used. Our power analysis anticipated AF freedom in 60% of CA and 65% of LFM+AAD patients; the study was not adequately powered to consider other acceptable scenarios of AF freedom for noninferiority (eg, 55% vs 60%). The LFM+AAD group was targeted toward dedicated weight reduction (which also included reduced alcohol consumption) and increased physical activity; other risk factors, such as tobacco use, obstructive sleep apnea, and more strict blood pressure control, were managed as part of standard care by the study's cardiologists. Exercise activity was not meticulously monitored.

CONCLUSIONS

Despite the significant positive benefits of LFM programs, CA was superior to LFM combined with AADs in terms of AF freedom at 1 year. Therefore, the referral to CA in this population should not be delayed until the patient loses weight. Nonetheless, patients with obesity should not be discouraged from losing weight, because several other significant benefits are associated with weight reduction.

DATA AVAILABILITY. The data supporting this study's findings are available from the corresponding author (Dr Osmancik) on reasonable request (eg, for meta-analyses).

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ADDRESS FOR CORRESPONDENCE: Dr Pavel Osmancik, Cardiocenter, Charles University Prague and University Hospital Kralovske Vinohrady, Department of Cardiology, Srobarova 50, 10034 Prague, Czech Republic. E-mail: pavel.osmancik@gmail.com.

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APPENDIX For supplemental material, please see the online version of this paper.