Circulation

ORIGINAL RESEARCH ARTICLE

Randomized Ablation-Based Rhythm-Control Versus Rate-Control Trial in Patients With Heart Failure and Atrial Fibrillation: Results from the RAFT-AF trial

Ratika Parkash, MD, MSc; George A. Wells, PhD; Jean Rouleau, MD; Mario Talajic, MD; Vidal Essebag, MD, PhD; Allan Skanes, MD; Stephen B. Wilton, MD, MSc; Atul Verma, MD; Jeffrey S. Healey, MD, MSc; Laurence Sterns, MD; Matthew Bennett, MD; Jean-Francois Roux, MD; Lena Rivard, MD; Peter Leong-Sit, MD; Mats Jensen-Urstad, MD; Umjeet Jolly, MD; Francois Philippon, MD; John L. Sapp, MD; Anthony S.L. Tang, MD

BACKGROUND: Atrial fibrillation (AF) and heart failure (HF) frequently coexist and can be challenging to treat. Pharmacologically based rhythm control of AF has not proven to be superior to rate control. Ablation-based rhythm control was compared with rate control to evaluate if clinical outcomes in patients with HF and AF could be improved.

METHODS: This was a multicenter, open-label trial with blinded outcome evaluation using a central adjudication committee. Patients with high-burden paroxysmal (>4 episodes in 6 months) or persistent (duration <3 years) AF, New York Heart Association class II to III HF, and elevated NT-proBNP (N-terminal pro brain natriuretic peptide) were randomly assigned to ablation-based rhythm control or rate control. The primary outcome was a composite of all-cause mortality and all HF events, with a minimum follow-up of 2 years. Secondary outcomes included left ventricular ejection fraction, 6-minute walk test, and NT-proBNP. Quality of life was measured using the Minnesota Living With Heart Failure Questionnaire and the AF Effect on Quality of Life. The primary analysis was time-to-event using Cox proportional hazards modeling. The trial was stopped early because of a determination of apparent futility by the Data Safety Monitoring Committee.

RESULTS: From December 1, 2011, to January 20, 2018, 411 patients were randomly assigned to ablation-based rhythm control (n=214) or rate control (n=197). The primary outcome occurred in 50 (23.4%) patients in the ablation-based rhythm-control group and 64 (32.5%) patients in the rate-control group (hazard ratio, 0.71 [95% CI, 0.49–1.03]; P=0.066). Left ventricular ejection fraction increased in the ablation-based group (10.1±1.2% versus 3.8±1.2%, P=0.017), 6-minute walk distance improved (44.9±9.1 m versus 27.5±9.7 m, P=0.025), and NT-proBNP demonstrated a decrease (mean change −77.1% versus −39.2%, P<0.0001). Minnesota Living With Heart Failure Questionnaire demonstrated greater improvement in the ablation-based rhythm-control group (least-squares mean difference of −5.4 [95% CI, −10.5 to −0.3]; P=0.0036), as did the AF Effect on Quality of Life score (least-squares mean difference of 6.2 [95% CI, 1.7–10.7]; P=0.0005). Serious adverse events were observed in 50% of patients in both treatment groups.

CONCLUSIONS: In patients with high-burden AF and HF, there was no statistical difference in all-cause mortality or HF events with ablation-based rhythm control versus rate control; however, there was a nonsignificant trend for improved outcomes with ablation-based rhythm control over rate control.

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Key Words: atrial fibrillation ■ catheter ablation ■ heart failure ■ mortality

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Correspondence to: Ratika Parkash, MD, MSc, Queen Elizabeth II Health Sciences Centre, 1796 Summer Street, Room 2501A, Halifax, Nova Scotia, Canada B3H 3A7; or Anthony S.L. Tang, MD, C6-116, University Hospital, London Health Sciences Centre, 339 Windermere Road, London, Ontario N6A 5A5. Email ratika.parkash@nshealth.ca or anthonysltang@gmail.com

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Clinical Perspective

What Is New?

- The RAFT-AF study (Rhythm Control - Catheter Ablation With or Without Anti-arrhythmic Drug Control of Maintaining Sinus Rhythm Versus Rate Control With Medical Therapy and/or Atrio-ventricular Junction Ablation and Pacemaker Treatment for Atrial Fibrillation) is a trial to determine if catheter ablation–based rhythm control, compared with rate control, affects all-cause mortality and heart failure events in patients with atrial fibrillation and heart failure.
- The trial, terminated early because of apparent futility, demonstrated no difference in all-cause mortality and heart failure events in the ablation-based rhythm-control group compared with rate control.
- Selected secondary outcomes, although exploratory, demonstrated improvement in ejection fraction, quality of life, NT-proBNP (N-terminal pro brain natriuretic peptide), and exercise tolerance with ablation-based rhythm control.

What Are the Clinical Implications?

- This study warrants additional investigation for ablation-based rhythm control for the treatment of atrial fibrillation and heart failure, which may reduce mortality and heart failure events.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
HF	heart failure
HR	hazard ratio
LSMD	least-squares mean difference
LVEF	left ventricular ejection fraction
NT-proBNP	N-terminal pro brain natriuretic peptide

Atrial fibrillation (AF) and heart failure (HF) frequently coexist and remain challenging to treat.[1] Pharmacological therapy to suppress AF is limited by significant side effects, including proarrhythmic risk and an association with increased mortality, in particular, in patients with HF.[2–4] Medication-based AF rhythm-control trials have shown no clinical benefit compared with rate control.[5,6] Potential reasons for this may be attributable to the inability to maintain sinus rhythm, the adverse effects of these medications, or inadequate use of oral anticoagulation. Catheter ablation for AF has been demonstrated to be more effective than medical therapy (rate or rhythm control) to reduce AF recurrence in patients with and without HF; in patients with reduced left ventricular function implanted with a defibrillator, catheter ablation of AF has also been shown to reduce HF hospitalizations and all-cause mortality.[7–17]

The RAFT-AF study (Rhythm Control– Catheter Ablation With or Without Anti-arrhythmic Drug Control of Maintaining Sinus Rhythm Versus Rate Control With Medical Therapy and/or Atrio-ventricular Junction Ablation and Pacemaker Treatment for Atrial Fibrillation) was initiated to determine whether AF therapy with ablation-based rhythm control with or without adjunctive antiarrhythmic medications changes all-cause mortality and HF events compared with aggressive rate control in patients with New York Heart Association class II and III HF with impaired or preserved left ventricular function and high-burden AF. The hypothesis was that AF is an instigator for HF and that a reduction in AF burden with ablation-based rhythm control compared with rate control will reduce mortality and HF events in both patients who have HF with reduced ejection fraction and HF with preserved ejection fraction.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design and Participants

RAFT-AF is a randomized controlled trial that enrolled patients from 21 acute care institutions from Brazil, Canada, Sweden, and Taiwan. The trial rationale and design have been previously described.[18] The steering and executive committees oversaw trial design and conduct, and the Data Monitoring Committee monitored trial conduct, safety, and efficacy. Data management and analysis was performed by the Cardiovascular Research Methods Center (University of Ottawa). The trial protocol was approved by institutional ethics review committees, and all patients provided written informed consent to participate.

Eligible patients with high-burden paroxysmal/persistent AF, New York Heart Association class II/III HF on optimal guideline-directed medical therapy and elevated NT-proBNP (N-terminal pro brain natriuretic peptide) were included.[19] High-burden paroxysmal AF was defined as ≥4 episodes of AF in the past 6 months, and at least 1 episode >6 hours (and no other episodes that required cardioversion or was >7 days); persistent AF (type 1) was defined as ≥4 episodes of AF in the past 6 months, and at least 1 episode >6 hours, and at least 1 AF episode <7 days, but requiring cardioversion with no AF episodes >7 days; persistent AF (type 2) was defined as at least 1 episode of AF >7 days but not >1 year; long-lasting persistent AF was defined as at least 1 AF episode >1 year and no episode >3 years. If the patient had not been hospitalized for HF in the previous 9 months, NT-proBNP was required to be ≥600 pg/mL if in sinus rhythm, or ≥900 pg/mL if in AF. If the patient had been hospitalized with HF in the past 9 months, NT-proBNP was required to be ≥400 pg/mL if in sinus rhythm or ≥600 pg/mL if in AF. Patients with left atrial dimension >55 mm, rheumatic heart disease, severe aortic or mitral valve disease, or life expectancy of <1 year were excluded. Detailed eligibility criteria are listed in Table S1. Optimal medical therapy is detailed in Table S2.

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Randomization and Masking

Participants were randomly allocated in a 1:1 ratio to ablation-based rhythm control or rate control. Central web-based randomization with permuted balanced blocks of 4 or 6 was used. Randomization was stratified by center, by left ventricular ejection fraction (LVEF) ≤45% or >45% and by AF type. Patients or treating physicians were not blinded to treatment allocation. All outcomes were adjudicated by a committee blinded to treatment allocation.

Procedures

For patients randomly assigned to ablation-based rhythm-control, centers adhered to practice guidelines for periablation procedures.[20] All antiarrhythmic medications were discontinued for 5 half-lives and amiodarone for 6 weeks before the procedure. Pulmonary vein isolation was the required minimum lesion set to be delivered; those with persistent AF underwent additional ablation that may have included ablation of complex fractionated atrial electrograms, roof line, mitral isthmus line, left atrial posterior wall isolation, or combinations thereof.[21] Antiarrhythmic medications were permitted for 4 to 6 weeks postablation and could thereafter only be used as adjunctive therapy for AF suppression after at least 2 ablation procedures. Antiarrhythmic medications used were amiodarone or dofetilide in patients with reduced left ventricular function and amiodarone or sotalol in patients with preserved left ventricular function. Further details are provided in Figure S1.

For patients randomly assigned to rate control, β-blockers, calcium channel blockers (if not contraindicated), digitalis, or in combination were used to achieve a resting heart rate <80 beats per minute and <110 beats per minute during a 6-minute walk. If heart rate was not controlled with medication, atrioventricular node ablation with biventricular pacing was recommended. Cardioversions or antiarrhythmic medications were not permitted except for the treatment of ventricular arrhythmias (Figure S2).

All patients in both groups were recommended to be maintained on oral anticoagulation indefinitely, irrespective of treatment assignment or outcome. At baseline and at each follow-up visit, all patients had a 12-lead ECG, 6-minute walk test, medication evaluation, and quality-of-life assessment with Minnesota Living With HF Questionnaire,[22] EQ5D-3 L, the AF Effect on Quality-of–Life,[23,24] and the Canadian Cardiovascular Society Severity in AF scale.[25] (For details, see Table S3.) In 7 centers, echocardiograms, NT-proBNP, and 14-day ambulatory monitoring (CardioSTAT) were to be obtained at 12 and 24 months. The echocardiograms and ambulatory monitoring were both adjudicated by core laboratories blinded to treatment assignment. For all patients, rhythm status was determined using the 12-lead ECG performed at each follow-up. LVEF was collected at the annual follow-up. All patients were followed at 2, 4, and 6 months, and then every 6 months for a minimum of 2 years, or until the end of follow-up.

Outcomes

The primary outcome was a composite of all-cause mortality and HF events defined as an admission to a health care facility for >24 hours or clinically significant worsening HF leading to the administration of intravenous diuretic in an emergency department or unscheduled visit to a health care provider, and an increase in chronic HF therapy.[26] Secondary outcomes included all-cause mortality; HF events; change in LVEF, NT-proBNP, 6-minute walk distance, and quality of life at 12 and 24 months. The composite primary outcome was evaluated in patients with LVEF ≤45% and >45%. The primary outcome events were adjudicated by an independent events committee, blinded to the randomized group using prospectively defined outcomes, as indicated earlier. Adverse events were collected as defined in the following: Any untoward medical occurrence in a patient or clinical investigation participants that did not necessarily have to have a causal relationship with this treatment. A serious adverse event was defined as an adverse reaction that results in death, was life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, or was a birth defect. The collection of serious adverse events commenced after randomization. For patients in the rate-control arm, admission to the hospital for an atrioventricular node ablation was not considered a serious adverse event. For patients in the ablation-based rhythm-control arm, admission to the hospital for a redo AF ablation was not considered a serious adverse event.

Statistical Analysis

All analyses were performed with the intention-to-treat principle. A minimal clinically important difference of 30% was determined by polling of clinicians before the initiation of the trial, who indicated that a minimum of 30% risk reduction was required to consider adopting an invasive therapy. A sample size of 600 patients (300 per group) was determined to detect a 30% relative risk reduction in the primary outcome in the catheter ablation-based rhythm-control group, with 80% power and a 2-sided significance of 0.05, assuming an annual event rate of 17% in the rate-control group. A total of 270 primary outcome events were expected. This calculation was performed using the log-rank test with all patients followed to the primary outcome or termination of the study, allowed for a 2% loss to follow-up, a 2% crossover from each group, and an O'Brien Fleming alpha spending function factor of 1.02 to adjust the sample size for interim analysis. In June 2017, the Data Monitoring Committee reviewed the planned interim analysis when 33% of patients (n=209) were enrolled and followed for a minimum of 1 year. On the basis of that analysis, the Data Monitoring Committee requested that a futility analysis be conducted on all patients enrolled and followed until September 9, 2017. On September 25, 2017, the Data Monitoring Committee recommended that enrollment be terminated and follow-up be continued for a minimum of 2 years for all patients. This decision was based on lower-than-expected enrollment and perceived futility. Data available on all 363 patients enrolled up to that time with follow-up for a median of 19.5 months were used to calculate a futility index of 0.81 for the primary outcome (PASS version 13) on the basis of the conditional power of 19%, defined as the probability of obtaining a statistically significant result if the study was continued to its planned completion (see Supplemental Material).

Kaplan-Meier product-limit estimates were used to summarize the time-to-outcome of each treatment groups and nonparametric log-rank tests to compare the time-to-outcome curves. Hazard ratios (HRs) and 95% CIs were calculated

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Table 1. Baseline Characteristics

Characteristics	Rate control (n=197)	Ablation-based rhythm control (n=214)
Age, y, mean±SD	67.5±8.0	65.9±8.6
Female sex, n (%)	49 (24.9)	57 (26.6)
Race, n (%)		
Asian	3 (1.5)	6 (2.8)
Black	0	2 (0.9)
White	193 (98.0)	204 (95.3)
Other	1 (0.5)	2 (0.9)
Body mass index, mean±SD	30.7±6.7	30.1±6.5
Underlying heart disease, n (%)		
Ischemic	55 (27.9)	74 (34.6)
Nonischemic	142 (72.1)	140 (65.4)
New York Heart Association class, n (%)		
II	131 (66.5)	144 (67.3)
III	66 (33.5)	70 (32.7)
Time from first diagnosis of AF, mo, median (Q1, Q3)	15 (6, 48)	14.5 (7, 36)
AF type, n (%)		
High-burden paroxysmal	11 (5.6)	19 (8.9)
Persistent type 1: AF <7 days but previous cardioversion	9 (4.6)	7 (3.3)
Persistent type 2: AF ≥7 days	129 (65.5)	140 (65.4)
Long-lasting persistent AF ≥1 y	48 (24.4)	48 (22.4)
Previous cardioversion, n (%)	116 (58.9)	114 (53.3)
Cardiac implanted electric devices (all)	67 (34.0)	68 (31.8)
Implantable cardioverter defibrillator	27 (13.7)	25 (11.7)
Pacemaker	15 (7.6)	14 (6.5)
CRT-P	1 (0.5)	7 (3.3)
CRT-D	24 (12.2)	22 (10.3)
Previous coronary revascularization (coronary artery bypass graft surgery/percutaneous coronary intervention), n (%)	45 (22.8)	64 (29.9)
Hospitalization for heart failure in the previous 9 mo, n (%)	60 (30.5)	71 (33.2)
CHA_2DS_2-VASc* score, n (%)		
1	27 (13.7)	26 (12.2)
2	31 (15.7)	47 (22.0)
3	52 (26.4)	53 (24.8)
4	42 (21.3)	44 (20.6)
5	29 (14.7)	36 (16.8)
≥6	16 (8.2)	8 (3.8)
6-min walk distance, mean±SD	344.4±107.1	363.1±101.4
NT-proBNP, median (Q1, Q3) ρg/mL	1583 (1041, 2641)	1689 (1000, 2743)
Medications, n (%)		
Previous or current antiarrhythmic medication	77 (39.1)	94 (43.9)
Mineralocorticoid receptor antagonist	53 (26.9)	51 (23.8)
Diuretics oral	140 (71.1)	158 (73.8)
β-Blocker	182 (92.4)	197 (92.1)
Digoxin	65 (33.0)	55 (25.7)
Calcium channel blocker	46 (23.4)	47 (22.0)
Statin	106 (53.8)	110 (51.4)
Angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker	161 (81.7)	155 (72.4)
Oral anticoagulant use, total n (%)	187 (94.9)	203 (94.9)
Warfarin	63 (32.0)	55 (25.7)
Direct oral anticoagulant	124 (62.9)	149 (69.6)
Other comorbidities, n (%)		
Hypertension	132 (67.0)	140 (65.4)
Chronic obstructive pulmonary disease	14 (7.1)	19 (8.9)
Diabetes	64 (32.5)	61 (28.5)
Stroke/transient ischemic attack	20 (10.2)	19 (8.9)
Current tobacco use, n (%)	12 (6.1)	18 (8.4)
No. of alcoholic drinks per wk with >14 for men or >7 for women	14 (7.1)	12 (5.6)
Left atrial diameter, mm, mean±SD	46.8±5.4 (n=195)	46.1±6.0 (n=212)
Left ventricular ejection fraction, n (%); mean±SD		
Ejection fraction ≤45%	116 (58.9); 30.3±9.2	124 (57.9); 30.1±8.5
Ejection fraction >45%	81 (41.1); 54.6±7.3	90 (42.1); 55.9±6.7

AF indicates atrial fibrillation; CRT, cardiac resynchronization therapy; D, defibrillator; P, pacemaker; and NT-proBNP, N-terminal pro brain natriuretic peptide.

*CHA_2DS_2-VASc is a score with 1 point assigned for each of the following: congestive heart failure, hypertension, age ≥65 years, age ≥75 years, diabetes, stroke (2 points), vascular disease, female sex.

using Cox proportional hazards modeling. The proportional hazards assumption was assessed using graphical (ie, visual inspection of the log-negative-log plot) and numeric tests (ie, test of the interaction term group×time). Where appropriate, a competing risk analysis was performed with mortality as the competing risk using the subdistribution hazard model proposed by Fine and Gray to analyze the secondary outcomes including HF events, change in LVEF, NT-proBNP, 6-minute walk distance, and quality of life. A priori subgroups were compared and $P_{interaction}$ values were calculated. Changes in secondary outcomes with continuous measures at visits 12 and 24 months from baseline were primarily analyzed with a mixed-effects model for repeated measures, including the study group as a between factor, visit as a within factor and study group by time interaction. As a secondary analysis, joint modeling of the repeated measures of these outcomes using time to mortality as a competing risk was conducted to evaluate the changes in these outcomes and the corresponding *P* value of

these changes between treatment groups was calculated.[27] A post hoc analysis was performed using the proportional means regression model for recurrent data.[28] The Wald test was used to determine statistical significance in this model. All tests were conducted at an α-level of 0.05. The analyses were performed with the use of SAS software, version 9.4 (SAS Institute). The trial was registered at https://www.clinicaltrials.gov; Unique identifier NCT01420393.

RESULTS

Patients and Therapy Allocation

Between December 1, 2011, and January 20, 2018, 411 patients were recruited from 21 centers in 4 countries (Table S4). The clinical characteristics at baseline did not differ between the groups (Table 1). Median follow-up was 37.4 months (Q1, Q3: 24.7, 53.7). Of 214 patients randomly assigned to the ablation-based rhythm-control group, 205 (95.7%) had catheter ablation; 4 patients refused, 2 had a persistent left atrial thrombus, and 3 did not undergo ablation because of venous access complications. Seven of these 9 patients received no ablation-based therapy; one was treated with an antiarrhythmic medication and one withdrew immediately after randomization (Figure 1). All 9 of these patients were included in the intention-to-treat analysis in the ablation-based rhythm-control group. All 197 patients in the rate-control group received the allocated intervention. Two patients in the ablation-based rhythm-control group and 5 in the rate-control group withdrew. Three patients in the ablation group and 4 in the rate-control group were lost to follow-up. Two patients underwent cardiac transplantation in the rate-control group. All patients enrolled contributed to the final analysis; those lost to follow-up, those who underwent transplantation, or those who withdrew were censored. There were 128 (62.4%) that had 1 ablation procedure, 69 (33.7%) had 2 procedures, and 8 (3.9%) underwent 3 procedures (Table S5). In the ablation-based rhythm-control group, 86.5% and 85.6% at the 12- and 24-month follow-up were in sinus rhythm, compared with 10.1% and 12.9% in the rate-control group (Figure 2). In the rate-control group, the mean resting heart rate in beats per minute was 74.3±11.8 at 12 months and 74.7±11.8 at 24 months. During the 6-minute walk, the heart rates were 88.7±15.2 and 87.4±14.4 at 12 and 24 months. There were 60 patients in the rate-control group who underwent atrioventricular node ablation and permanent pacing. Use of optimal medical therapy for HF was consistent throughout the study. Oral anticoagulation use was 95%.

Outcomes

The primary outcome of all-cause mortality or HF event occurred in 50 of 214 (23.4%) in the ablation-based rhythm-control group compared with 64 of 197 (32.5%) in the rate-control group (HR, 0.71 [95% CI, 0.49–1.03]; *P*=0.066; Table 2, Figure 3). The proportional hazards assumption was confirmed. All-cause mortality was 29 (13.6%) in the ablation-based rhythm-control group, 34 (17.3%) in the rate-control group (HR, 0.79 [95% CI, 0.48–1.30]; *P*=0.349; Table 2; Figure S3). Total HF events occurred in 38 (17.8%) in the ablation-based rhythm-control group, 48 (24.4%) in the rate-control group (HR, 0.71 [95%CI, 0.47-1.09]; *P*=0.120). The cumulative incidence of HF events using competing risk analysis is shown in Figure S4.

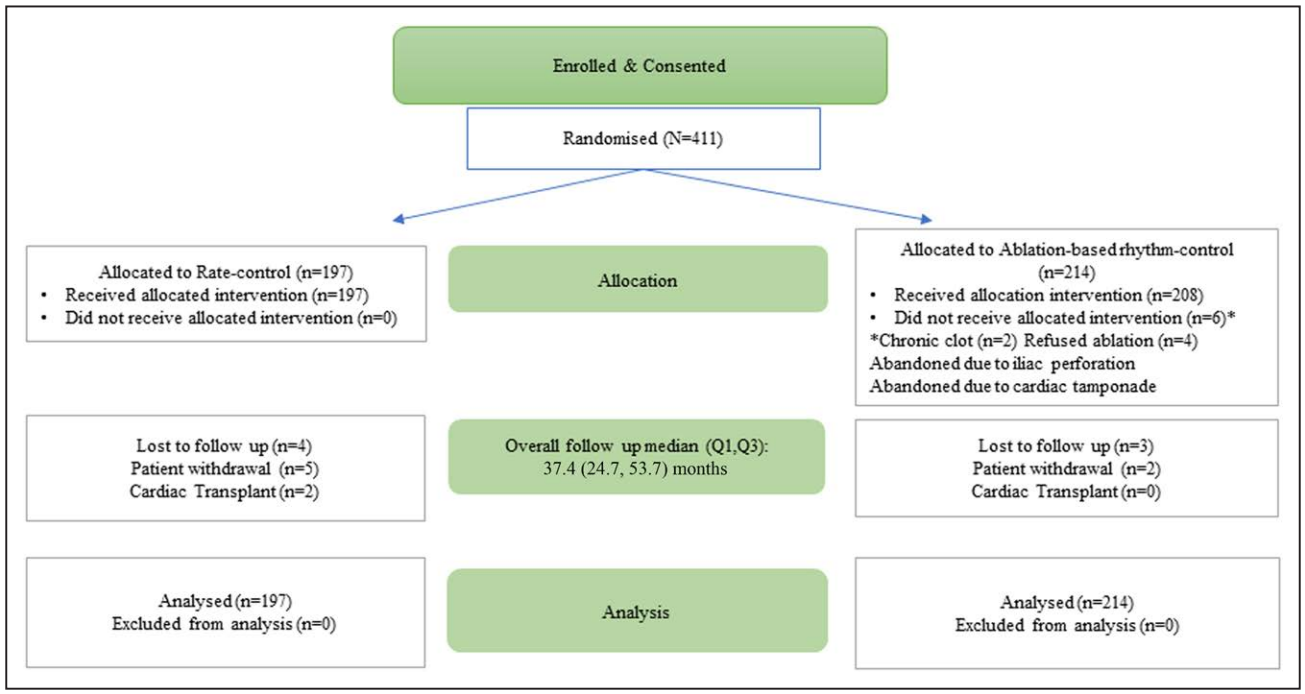

Figure 1. Patient flow.

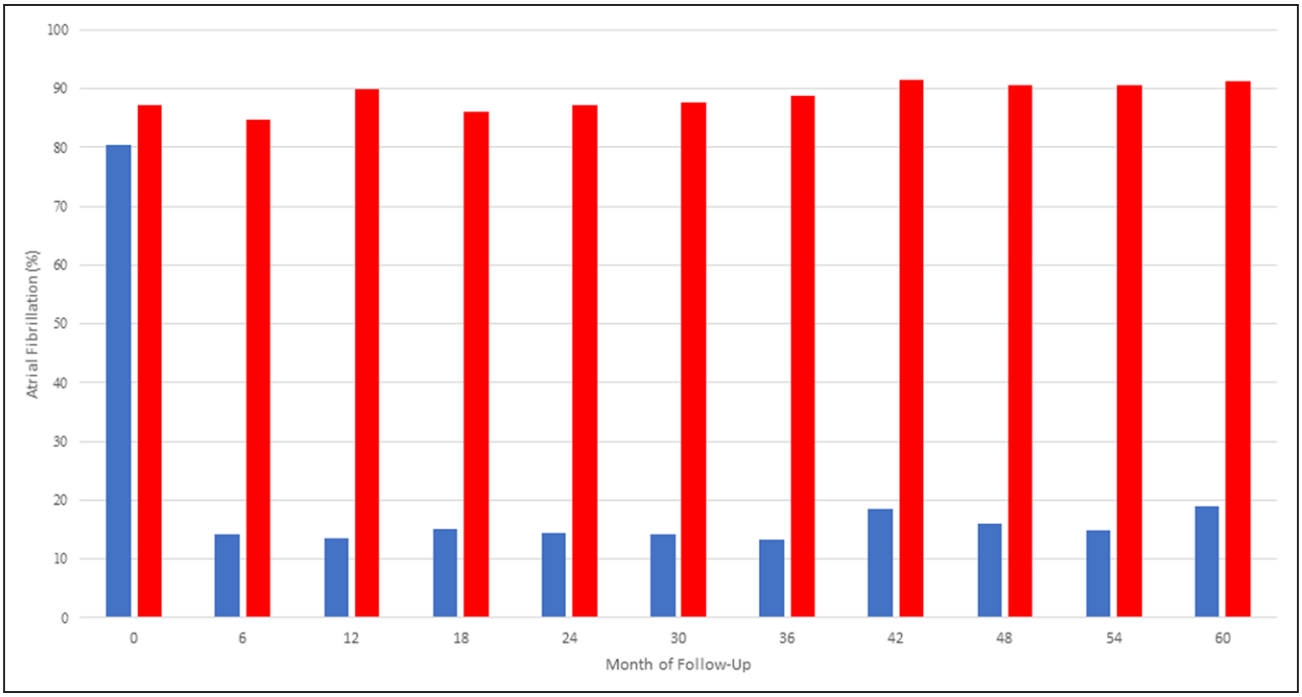

Figure 2. Presence of atrial fibrillation on 12-lead ECG at each follow-up in each group.
There is a significant reduction in the occurrence of atrial fibrillation in the ablation-based rhythm control that is sustained. In the ablation-based rhythm-control group, 86.5% and 85.6% of patients at the 12- and 24-month follow-up, respectively, were in sinus rhythm, compared with 10.1% and 12.9% in the rate-control group. The blue bars indicate the ablation-based rhythm-control group; and the red bars, the rate-control group.

There was a greater increase of LVEF over time in the ablation-based rhythm-control group compared with the rate-control group after accounting for competing risk of mortality (see Table 2; Figure S5). A sustained increase in LVEF at 24 months of 10.1±1.2% in the ablation-based rhythm-control group compared with 3.8±1.2% in the rate-control group at 24 months (least-squares mean difference [LSMD] of 6.9% [95% CI, 3.5–10.3]; *P*=0.017) was found. Disease-specific quality-of-life scales for HF and AF improved in both treatment groups, but to a greater degree in the ablation-based rhythm-control group (Table 2; Figure S6A and S6B). The Minnesota Living With HF Questionnaire demonstrated an improvement in both groups at 12 and 24 months, but to a greater degree in the ablation-based rhythm-control group (LSMD of −5.4 [95% CI, −10.5 to −0.3]; *P*=0.0036). AF Effect on Quality-of–Life similarly improved in both groups but to a greater degree in the ablation-based rhythm-control group (LSMD of 6.2 [95% CI, 1.7–10.7]; *P*=0.0005). Six-minute walk distance improved by 44.9±9.1 m in the ablation-based group at 24 months compared with 27.5±9.7 m in the rate-control group (LSMD of 34.2 m [95% CI, 9.3–59.1]; *P*=0.025; Figure S7). NT-proBNP demonstrated a −77.1% (95% CI, −86.3 to −67.9) mean change at 24 months in the ablation-based rhythm-control group compared with a mean change of −39.2% (95% CI, −50.9 to −27.5) in the rate-control group (LSMD of −37.9% [95% CI, −51.2 to −22.1]; *P*<0.0001; Figure S8). At the last follow-up, 94.6% of patients in the ablation-based rhythm-control group and 95.9% in the rate-control group were on oral anticoagulation; antiarrhythmic medications were used in 22.8% of the ablation-based rhythm-control group and 6.2% of the rate-control group. Optimal medical therapy remained consistent throughout the study (Table S6).

A post hoc competing events analysis was performed to examine for recurrent HF events, with the competing event being mortality. This analysis did not find any significant differences between the 2 groups (HR, 0.71 [95% CI, 0.46–1.08]; *P*=0.107; Figure S9A and S9A)

Adverse Events

The number of patients with ≥1 serious adverse events were 102 (47.7%) in the ablation-based rhythm-control group and 99 (50.3%) in the rate-control group (Table S7). The total number of hospitalizations in the ablation-based rhythm-control group was 261 (mean, 2.6 [95% CI, 2.1–3.0]) and 233 (mean, 2.4 [95% CI, 2.0–2.7]) in the rate-control group (relative risk, 1.03 [95% CI, 0.86–1.23]; *P*=0.733). Ablation-related serious adverse events included 1 patient with atrioesophageal fistula that led to death, 6 pericardial effusions requiring pericardiocentesis, 8 major bleeding events, and 5 minor bleeding events. In the rate-control group, 4 patients experienced bradycardia and 1 patient had amiodarone-induced toxicity. Ten patients had a stroke, 5 from each treatment group. Four patients were on warfarin. Six patients were on direct oral anticoagulant, which was temporarily held in 3 of these patients.

Table 2. Primary and Key Secondary Efficacy Outcomes

All patients	Rate control (n=197)	Ablation-based rhythm control (n=214)	Treatment effect*	*P* value†
Primary outcome, n (%)				
All-cause mortality or heart failure event‡	64 (32.5)	50 (23.4)	0.71 (0.49 to 1.03)	0.066
Secondary outcomes§				
All-cause mortality	34 (17.3)	29 (13.6)	0.79 (0.48 to 1.30)	0.349
Heart failure events	48 (24.4)	38 (17.8)	0.71 (0.47 to 1.09)	0.120
Change from baseline in MLHFQ‖			−5.4 (−10.5 to −0.3)	0.0036
At 12 mo	−13.9±1.7	−20.1±1.6		
At 24 mo	−14.8±2.1	−17.4±2.1		
Change from baseline in AFEQT¶			6.2 (1.7 to 10.7)	0.0005
At 12 mo	16.1±1.6	23.4±1.5		
At 24 mo	18.9±2.0	23.8±1.9		
Change in 6-min walk distance (meters)#			34.2 (9.3 to 59.1)	0.025
At 12 mo	30.5±7.2	36.4±6.7		
At 24 mo	27.5±9.7	44.9±9.1		
Change in geometric mean NT-proBNP (%)			−37.9 (−51.2 to −22.1)	<0.0001
At 12 mo	−45.4 (−58.4 to −32.4)	−80.0 (−89.6 to −70.4)		
At 24 mo	−39.2 (−50.9 to −27.5)	−77.1 (−86.3 to −67.9)		
Change in left ventricular ejection fraction (%)			6.9 (3.5 to 10.3)	0.017
At 12 mo	4.1±1.0	7.7±0.9		
At 24 mo	3.8±1.2	10.1±1.2		

NT-proBNP indicates N-terminal pro brain natriuretic peptide.

*Treatment effect is reported as hazard ratio (HR) with 95% CI and as the least-squares mean difference with 95% CI.

†The *P* value reported for the secondary outcomes is from the joint model where competing risk of death is accounted for.

‡Heart failure event is defined as an admission to a health care facility for >24 hours OR clinically significant worsening heart failure leading to an intervention such as treatment in an emergency department, a same-day access clinic, or an infusion center OR unscheduled visits to a health care provider for administration of an intravenous diuretic, and an increase in chronic heart failure therapy.

§Changes of quality-of-life score, 6-minute walk distance, and left ventricular ejection fraction at 24 moths from baseline are expressed as the least-squares mean difference±SE using a repeated-measures, linear mixed-effects model including group, visit, and group×visit interaction. The percentage changes with 95% CI for the ratio of geometric means at 12 or 24 months to baseline are reported for NT-proBNP.

‖MLHFQ is the Minnesota Living with Heart Failure questionnaire, which is a self-administered disease-specific questionnaire for patients with heart failure, comprising 21 items rated on a 6-point Likert scale, representing different degrees of effect of heart failure on quality of life, from 0 (none) to 5 (very much). It provides a total score (range 0–105, from best to worst quality of life), a lower score indicating a better quality of life. The minimally clinically important difference ranges from 3.6 to 19.1 points.[22]

¶AFEQT is the AF Effect on Quality-of-Life survey, which is a disease-specific health-related quality-of-life instrument, range from 0 to 100, with higher scores indicating a better health-related quality of life. For AFEQT scales, a change of ≥19 is correlated with a minimally important difference in an individual patient.[24]

#A meaningful change in 6-minute walk distance is 32 meters.

Prespecified Subgroups

A prespecified analysis of the primary outcome by LVEF ≤45% and >45%, for which patients were stratified at randomization, was performed (for baseline characteristics of these 2 groups see Tables S8 and S9). The primary outcome occurred in 28 of 124 (22.6%) in the ablation-based rhythm-control group with LVEF ≤45% compared with 43 of 116 (37.1%) patients in the rate-control group (HR, 0.63 [95% CI, 0.39–1.02]; *P*=0.059, $P_{interaction}$ value=0.40; Figure S10A). In the LVEF >45% group, the primary outcome occurred in 22 of 90 (24.4%) in the ablation-based rhythm-control group compared with 21 of 81 (25.9%) in the rate-control group (HR, 0.88 [95% CI, 0.48–1.61]; *P*=0.672; Figure S10B).

AF Effect on Quality-of–Life, Minnesota Living With HF Questionnaire, 6-minute walk distance, LVEF, and NT-proBNP improved with ablation-based rhythm control in patients with LVEF ≤45% (Table 3). There was no difference in quality of life and 6-minute walk distance for patients with LVEF >45% between treatment strategies (Tables 3 and 4; Figures S5–S8); however, NT-proBNP decreased in the ablation-based rhythm-control group (LSMD of −29.3 [95% CI, −49.6 to −4.8]; *P*=0.020) compared with the rate-control group. There was an increase in LVEF over time with ablation-based rhythm control (LSMD of 7.6% [95% CI, 4.3–10.8]; *P*=0.008).

Analysis by AF type, which was stratified at the time of randomization, demonstrated a greater effect in the paroxysmal and early persistent AF group (<7 days) for ablation-based rhythm-control (HR, 0.24 [95% CI,

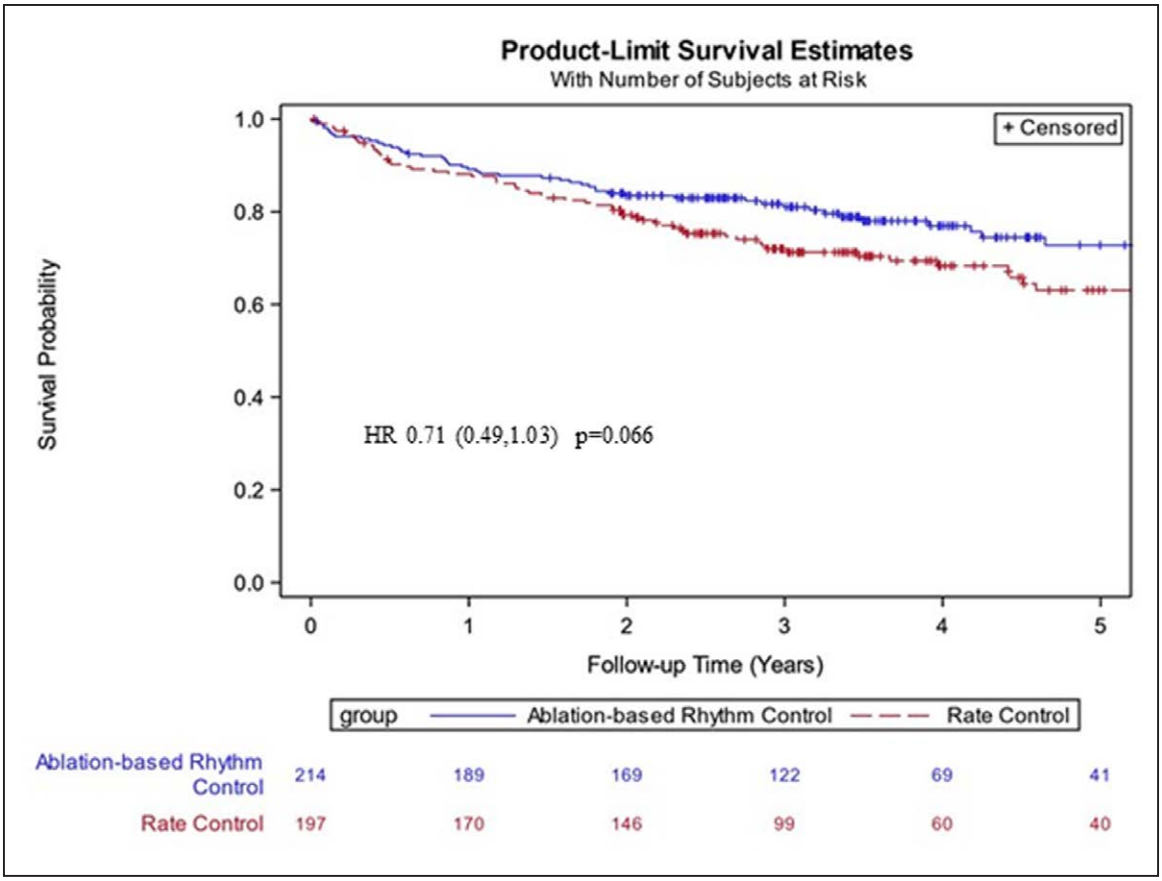

Figure 3. Freedom from all-cause mortality or heart failure event.
The blue line indicates the ablation-based rhythm-control group; the red line, the rate-control group; and HR, hazard ratio.

0.08–0.70]; $P_{interaction}$=0.171) compared with persistent AF (duration >7 days but <1 year; HR, 0.68 [95% CI, 0.43–1.09]) and long-term persistent AF (duration >1 year; HR, 1.13 [95% CI, 0.50–2.57]). Analysis by sex demonstrated a greater effect in women (HR, 0.42 [95% CI, 0.19–0.92]; $P_{interaction}$=0.077) compared with men (HR, 0.86 [95% CI, 0.48–1.32]). Other subgroup analyses are shown in Figure 4.

DISCUSSION

In this trial of patients with AF and HF, ablation-based rhythm control did not significantly affect the primary composite outcome compared with rate control. Patients in the ablation-based rhythm-control group had greater improvement in left ventricular function, improvement of quality of life, and reduced NT-proBNP. These results must be interpreted with caution in the context of the trial being stopped early because of apparent futility at the time of the interim analysis.

There are several possible explanations as to why statistical significance was not achieved in this study. It is possible that there is no benefit of ablation-based rhythm control over rate control on mortality and HF events. An alternate explanation is that the power to detect a statistically significant result was diminished, because fewer events occurred in the study than originally planned. The study enrollment was stopped early because of a perceived lack of a potential treatment effect of ablation-based rhythm control over rate control at the interim analysis. The differential occurrence of primary outcome events was realized only after 18 months of follow-up.

The secondary outcomes must be interpreted in the context of the early termination of the trial, but they appear to demonstrate benefit of ablation-based rhythm control over rate control. Quality-of-life measures specific for HF, and separate measures specific for AF, 6-minute walk distance, LVEF, and NT-proBNP demonstrated more improvement in patients with ablation-based rhythm control than in patients with rate control, after adjusting for the competing risk of death.

Previous studies have primarily focused on surrogate measures of HF such as LVEF and maximal oxygen consumption, or have measured AF recurrence.[7–17] The PABA-CHF study (Pulmonary Vein Antrum Isolation versus AV Node Ablation with Bi-Ventricular Pacing for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure) was the first study to demonstrate the improvement of LVEF in patients with LVEF ≤40% randomly assigned to atrioventricular nodal ablation

Table 3. Primary and Key Secondary Efficacy Outcomes by Left Ventricular Ejection Fraction ≤45%

Outcomes	Rate-control (n=116)	Ablation-based rhythm control (n=124)	Treatment effect (95%CI)*	*P* value†
Primary outcome, n (%)				
All-cause mortality or heart failure event‡	43 (37.1)	28 (22.6)	0.63 (0.39 to 1.02)	0.059
Secondary outcomes§				
Change in MLHFQ‖			−5.8 (−12.4 to 0.7)	0.012
At 12 mo	−15.6±2.1	−19.7±2.1		
At 24 mo	−16.7±2.7	−18.1±2.7		
Change in AFEQT¶			7.9 (2.4 to 13.5)	0.004
At 12 mo	17.8±2.0	20.3±2.5		
At 24 mo	23.9±1.9	25.4±2.4		
Change in 6-min walk distance (meters)#			41.1 (9.0 to 73.3)	0.024
At 12 mo	34.3±9.1	24.1±8.6		
At 24 mo	42.1±12.2	47.4±11.8		
Change in geometric mean NT-proBNP (%)			−44.0 (−60.1 to −23.1)	<0.0001
At 12 mo	−39.6 (−57.4 to −21.8)	−79.6 (−92.2 to −67.0)		
At 24 mo	−35.7 (−50.9 to −20.5)	−79.7 (−91.2 to −68.2)		
Change in left ventricular ejection fraction (%)			6.3 (2.7 to 9.9)	0.019
At 12 mo	8.2±1.2	12.2±1.1		
At 24 mo	8.4±1.4	14.9±1.4		

NT-proBNP indicates N-terminal pro brain natriuretic peptide.

*Treatment effect is reported as hazard ratio with 95% CI and as the least-squares mean difference with 95% CI.

†The *P* value reported for the secondary outcomes is from the joint model where competing risk of death is accounted for.

‡Heart failure event is defined as an admission to a health care facility for >24 hours OR clinically significant worsening heart failure leading to an intervention such as treatment in an emergency department, a same-day access clinic, or an infusion center OR unscheduled visits to a health care provider for administration of an intravenous diuretic, and an increase in chronic heart failure therapy.

§Changes of quality-of-life score, 6-minute walk distance, and left ventricular ejection fraction at 24 months from baseline are expressed as the least-square mean difference±SE using a repeated-measures, linear mixed-effects model including group, visit, and group×visit interaction. The percentage changes with 95% CI for the ratio of geometric means at 12 or 24 months to baseline are reported for NT-proBNP.

‖MLHFQ is the Minnesota Living with Heart Failure questionnaire, which is a self-administered disease-specific questionnaire for patients with heart failure, comprising 21 items rated on a 6-point Likert scale, representing different degrees of effect of heart failure on quality of life, from 0 (none) to 5 (very much). It provides a total score (range 0–105, from best to worst quality of life), a lower score indicating a better quality of life. The minimally clinically important difference ranges from 3.6 to 19.1 points.[22]

¶AFEQT is the AF Effect on Quality-of-Life survey, which is a disease-specific health-related quality-of-life instrument, range from 0 to 100, with higher scores indicating a better health-related quality of life. For AFEQT scales, a change of ≥19 is correlated with a minimally important difference in an individual patient.[24]

#A meaningful change in 6-minute walk distance is 32 meters.

with cardiac resynchronization therapy compared with pulmonary vein isolation.[7] The mean improvement in LVEF was 8%. Subsequent studies included patients with LVEF varying from <50% to <35%, comparing catheter ablation with pharmacological rate control or rhythm control with amiodarone. Improvements in LVEF, maximal oxygen consumption, and reduction in AF burden were demonstrated. The CASTLE-AF study (Catheter Ablation Versus Standard Conventional Treatment in Patients With Left Ventricular Dysfunction and AF) demonstrated that ablation of AF in patients who have HF with LVEF ≤35% and an implanted defibrillator reduced all-cause mortality and HF events with a HR of 0.62 over medication-based rate or rhythm control.[17] Some differences exist between CASTLE-AF and this study. The medical treatment group in CASTLE-AF included both rate- and medication-based rhythm control. Both studies, however, achieved marked and sustained reductions in AF with ablation-based rhythm control. This is in stark contrast to previous rate versus rhythm studies, where the maintenance of sinus rhythm ranged from 40% to 60% with antiarrhythmic medications.[5,6] In both studies, there was a time delay from the reduction of AF with catheter ablation to improvement in ventricular function and the manifestation of clinical benefit. Mortality curves did not separate for 2 years after study entry in the CASTLE-AF study. This delayed treatment effect may be attributable to the time course for left ventricular remodeling to occur after elimination of AF. In the PABA-CHF study, LVEF recovery continued to occur until the 6-month follow-up point. In addition, early recurrence of AF is common, and reduction in AF burden may not occur for 3 to 6 months after study entry, in particular, if repeat ablations are required. The use of ablation-based rhythm control in CASTLE-AF and this study results in greater reduction

Table 4. Primary and Key Secondary Efficacy Outcomes by Left Ventricular Ejection Fraction >45%

Outcomes	Rate-control (n=81)	Ablation-based rhythm control (n=90)	Treatment effect (95% CI)*	*P* value†
Primary outcome, n (%)				
All-cause mortality or heart failure event‡	21 (25.9)	22 (24.4)	0.88 (0.48 to 1.61)	0.672
Secondary outcomes§				
Change in MLHFQ‖			−4.6 (−12.6 to 3.4)	0.123
At 12 mo	−11.5±2.6	−20.7±2.5		
At 24 mo	−12.3±3.3	−16.3±3.3		
Change in AFEQT¶			3.9 (−3.4 to 11.2)	0.080
At 12 mo	13.6±2.6	22.9±2.4		
At 24 mo	16.9±3.2	21.8±3.1		
Change in 6-min walk distance (meters)#			25.2 (−14.1 to 64.4)	0.327
At 12 mo	24.7±11.6	53.2±10.7		
At 24 mo	5.7±15.9	40.9±14.3		
Change in geometric mean NT-proBNP (%)			−29.3 (−49.6 to −4.8)	0.020
At 12 mo	−49.3 (−68.2 to −30.4)	−80.8 (−95.4 to −66.2)		
At 24 mo	−44.1 (−62.2 to −26.0)	−73.4 (−88.5 to −58.3)		
Change in left ventricular ejection fraction (%)			7.6 (4.3 to 10.8)	0.008
At 12 mo	−2.0±1.2	1.3±1.0		
At 24 mo	−2.8±1.4	3.4±1.3		

NT-proBNP indicates N-terminal pro brain natriuretic peptide.

*Treatment effect is reported as hazard ratio with 95% CI and as the least-squares mean difference with 95% CI.

†The *P* value reported for the secondary outcomes is from the joint model where competing risk of death is accounted for.

‡ Heart failure event is defined as an admission to a health care facility for >24 hours OR clinically significant worsening heart failure leading to an intervention such as treatment in an emergency department, a same-day access clinic, or an infusion center OR unscheduled visits to a health care provider for administration of an intravenous diuretic, and an increase in chronic heart failure therapy.

§Changes of quality-of-life score, 6-minute walk distance, and left ventricular ejection fraction at 24 months from baseline are expressed as the least-square mean difference±SE using a repeated-measures, linear mixed-effects model including group, visit, and group×visit interaction. The percentage changes with 95% CI for the ratio of geometric means at 12 or 24 months to baseline are reported for NT-proBNP.

‖MLHFQ is the Minnesota Living with Heart Failure questionnaire, which is a self-administered disease-specific questionnaire for patients with heart failure, comprising 21 items rated on a 6-point Likert scale, representing different degrees of effect of heart failure on quality of life, from 0 (none) to 5 (very much). It provides a total score (range 0–105, from best to worst quality of life), a lower score indicating a better quality of life. The minimally clinically important difference ranges from 3.6 to 19.1 points.[22]

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#A meaningful change in 6-minute walk distance is 32 meters.

of AF burden and does not portend the long-term effects of antiarrhythmic medications. The ablation-related serious adverse events were of life-threatening variety, although the rate was not higher than observed in previous studies of catheter ablation in patients with or without HF.[29] This must be considered for the application of this therapy.

Study Limitations

This study has some additional limitations beyond what was discussed with respect to lack of power to detect a difference and the early termination of the trial. The ablation approach and techniques evolved over the period in which this study was undertaken, in particular, for persistent AF. Adjustment for multiple comparisons was not performed for secondary analyses; hence, these findings should be considered exploratory.

Conclusion

This trial did not show a statistically significant difference in all-cause mortality or HF events with ablation-based rhythm control over rate control in patients with high-burden AF and HF.

Perspectives

Competency in Medical Knowledge

Ablation-based rhythm control may provide improved clinical benefit in patients with high-burden AF and HF.

Competency in Patient Care

Patients with concomitant AF and HF should be evaluated for the appropriateness of ablation-based rhythm control to improve quality of life, LVEF, and HF biomarkers. It remains unclear if ablation-based rhythm control reduces HF events and death.

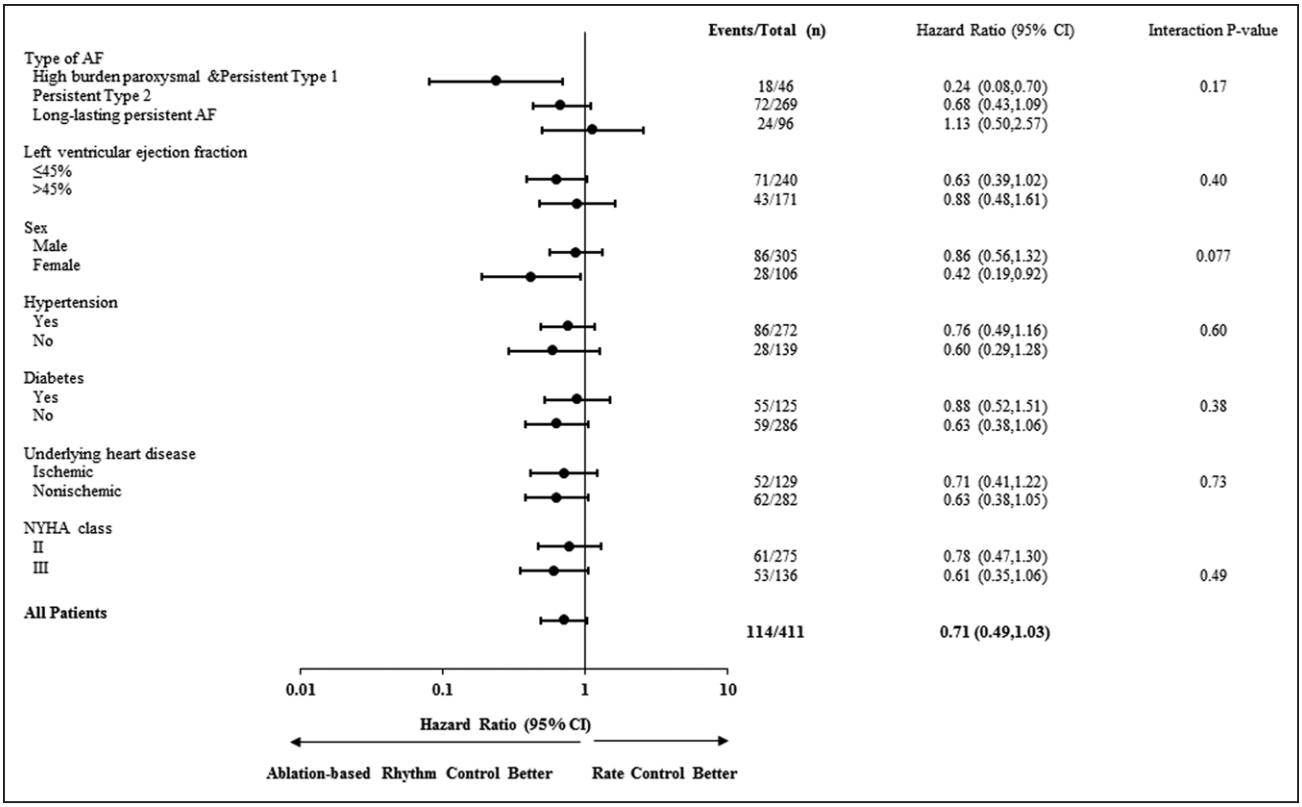

Figure 4. Prespecified subgroups.
AF indicates atrial fibrillation; and NYHA, New York Heart Association.

Translational Outlook

This study was stopped early because of the low recruitment rate and perceived lack of benefit. Longer-term follow-up may provide a better understanding of ablation-based rhythm control on HF events and mortality in patients with AF and HF.

ARTICLE INFORMATION

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Affiliations

Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada (R.P., J.L.S.). University of Ottawa Cardiovascular Research Methods Centre, Ontario, Canada (G.A.W.). Montréal Heart Institute, Université de Montréal, Québec, Canada (J.R., M.T., L.R.). McGill University Health Centre, Montreal, Québec, Canada (V.E.). Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada (A.S., P.L.-S., A.S.L.T.). Libin Cardiovascular Institute, University of Calgary, Alberta, Canada (S.B.W.). Southlake Regional Health Centre, Ontario, Canada (A.V.). Population Health Research Institute, Hamilton, Ontario, Canada (J.S.H.). Royal Jubilee Hospital, Island Health Authority, Victoria, British Columbia, Canada (L.S.). Centre for Cardiovascular Innovation, Division of Cardiology, University of British Columbia, Vancouver, Canada (M.B.). Centre Hospitalier de Universite de Sherbrooke, Sherbrooke, Québec, Canada (J.-F.R.). Karolinska Institute, Stockholm, Sweden (M.J.-U.). St. Mary's General Hospital, Kitchener, Ontario, Canada (U.J.). Institut universitaire de cardiologie et de pneumologie de Québec, Québec City, Canada (F.P.).

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Supplemental Material

List of Participating Centers
Expanded Methods
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Figures S1–S10

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