A Randomized Ablation-based atrial Fibrillation rhythm control versus rate control Trial in patients with heart failure and high burden Atrial Fibrillation

RAFT-AF

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Disclosure

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Anthony Tang Disclosure Information

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Hypothesis

Primary Hypothesis

- Catheter ablation-based AF rhythm control as compared with rate control reduces the primary outcome of all-cause mortality and HF events in patients with AF and HF of either LVEF ≤45% or LVEF >45%

Secondary Hypotheses

- Catheter ablation-based AF rhythm control as compared with rate control reduces the primary outcome of all-cause mortality and HF events in patients with AF and HF of LVEF ≤45%
- Catheter ablation-based AF rhythm control as compared with rate control reduces the primary outcome of all-cause mortality and HF events in patients with AF and HF of LVEF >45%

Study Design

- Parallel, randomized controlled trial
  - Eligible patients were randomly assigned in a 1:1 ratio to receive
    - Ablation-based rhythm control
    - Rate control
  - Stratified by center, LVEF (≤45%, >45%), and atrial fibrillation type
- 21 centres from Canada, Sweden, Brazil and Taiwan
- PROBE (Prospective Randomized Open Blinded End-point) design
- Trial Interventions:
  - Ablation-based rhythm control – one or more ablations for AF with Pulmonary Vein Isolation ± addition lesions; antiarrhythmic drug used for AF recurrence after more than one ablation procedures
  - Rate control – AV nodal blockers ± ablate and bi-V pace targeting a resting HR ≤80 bpm and post 6-minute walk HR ≤110 bpm

Key Inclusion Criteria

- Patients with one of the following AF type (at least one ECG of AF)
  1. High Burden Paroxysmal AF: ≥4 episodes of AF in the last 6 months, and at least one episode >6 hours (not required cardioversion) and was <7 days
  2. Persistent AF 1: AF episodes <7 days but requires cardioversion
  3. Persistent AF 2: at least one episode of AF >7 days but not >1 year
  4. Long-term Persistent AF: at least one episode >one year, but not <3 years
- Optimal therapy for heart failure of at least 6 weeks
- Heart failure with NYHA class II or III symptoms
- Either impaired LV function (LVEF ≤45%) or preserved LV function (LVEF >45%) determined within 12 months prior to enrollment
- Suitable candidate for catheter ablation or rate control for the treatment of AF
- Age ≥18
- NT-proBNP/BNP

Current rhythm	HF hospitalization in last 9 months	NT pro-BNP
AF	Yes	≥ 600 pg/mL
AF	No	≥ 900 pg/mL
Sinus	Yes	≥ 400 pg/mL
Sinus	No	≥ 600 pg/mL

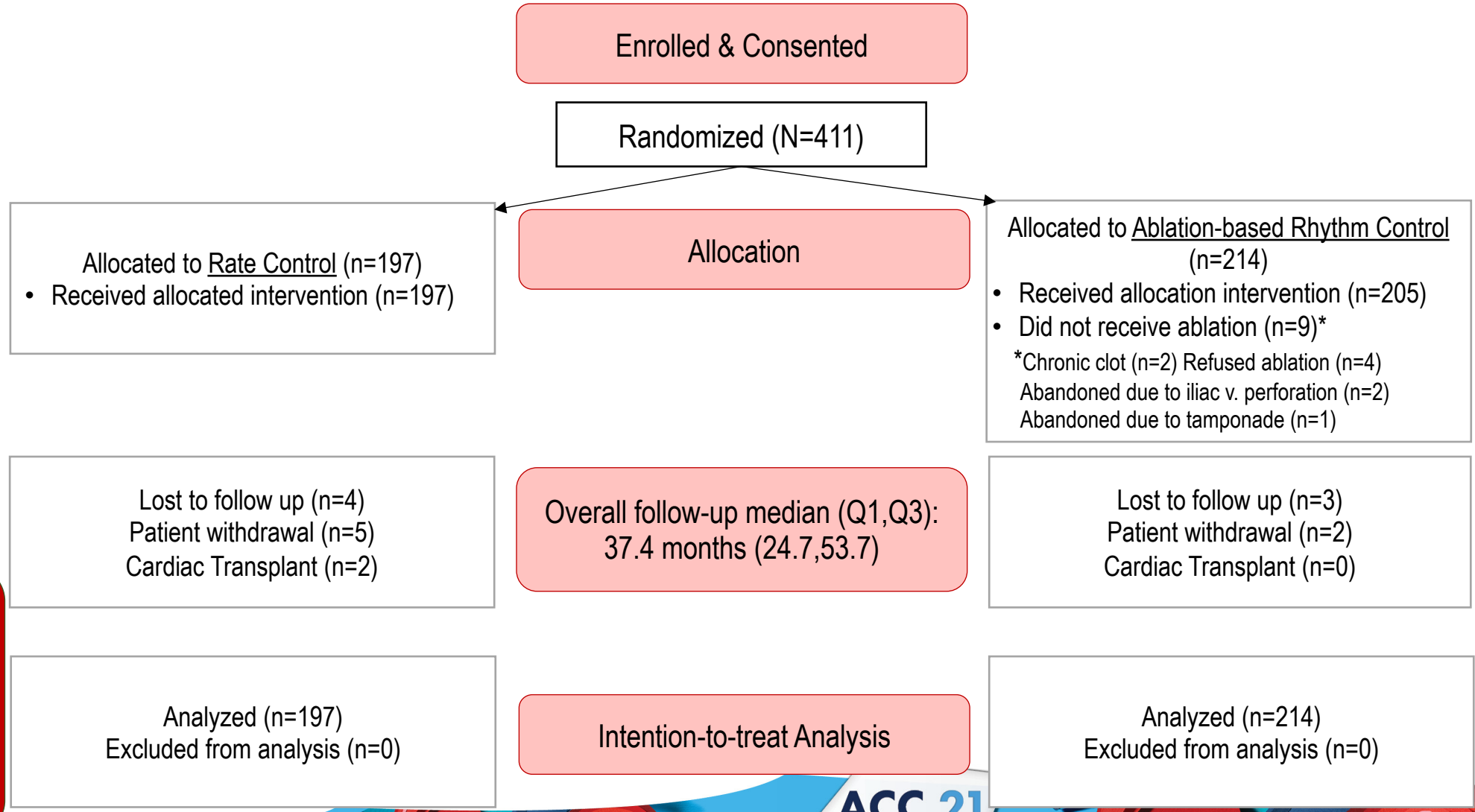
Primary and Secondary Outcome Measures

- **Primary Outcome: Composite of time to death or HF event**
  - HF event was defined as an admission to a healthcare facility for >24 hours OR clinically significant worsening HF leading to administration of an intravenous diuretic, and an increase in chronic HF therapy in an emergency department or unscheduled visit to a healthcare provider
- Secondary Outcomes: death, HF event, change in LVEF, NT-proBNP, six-minute walk distance, and quality of life at 12 and 24 months
- The primary and secondary outcomes were evaluated in patients with LVEF ≤45% and >45%.
- Subgroup analysis (not stratified): sex, diabetes, hypertension, underlying heart disease, NYHA class

Trial Progress

- Initial sample size was calculated to be 600 (300 per study group)
  - 30% relative risk reduction of the primary outcome
  - Annual event rate 17% in the rate control group, 11.9% in the rhythm control group
  - Loss of follow-up = 2%; crossover = 2%
- In January 2018, recruitment was stopped on the recommendation of the Data Monitoring Committee after the interim analysis due to
  - Lower than expected enrollment rate
  - Lower than expected event rate
  - Perceived futility, based on the data of 363 patients followed for a median of 19.5 months --- Futility index of 0.81

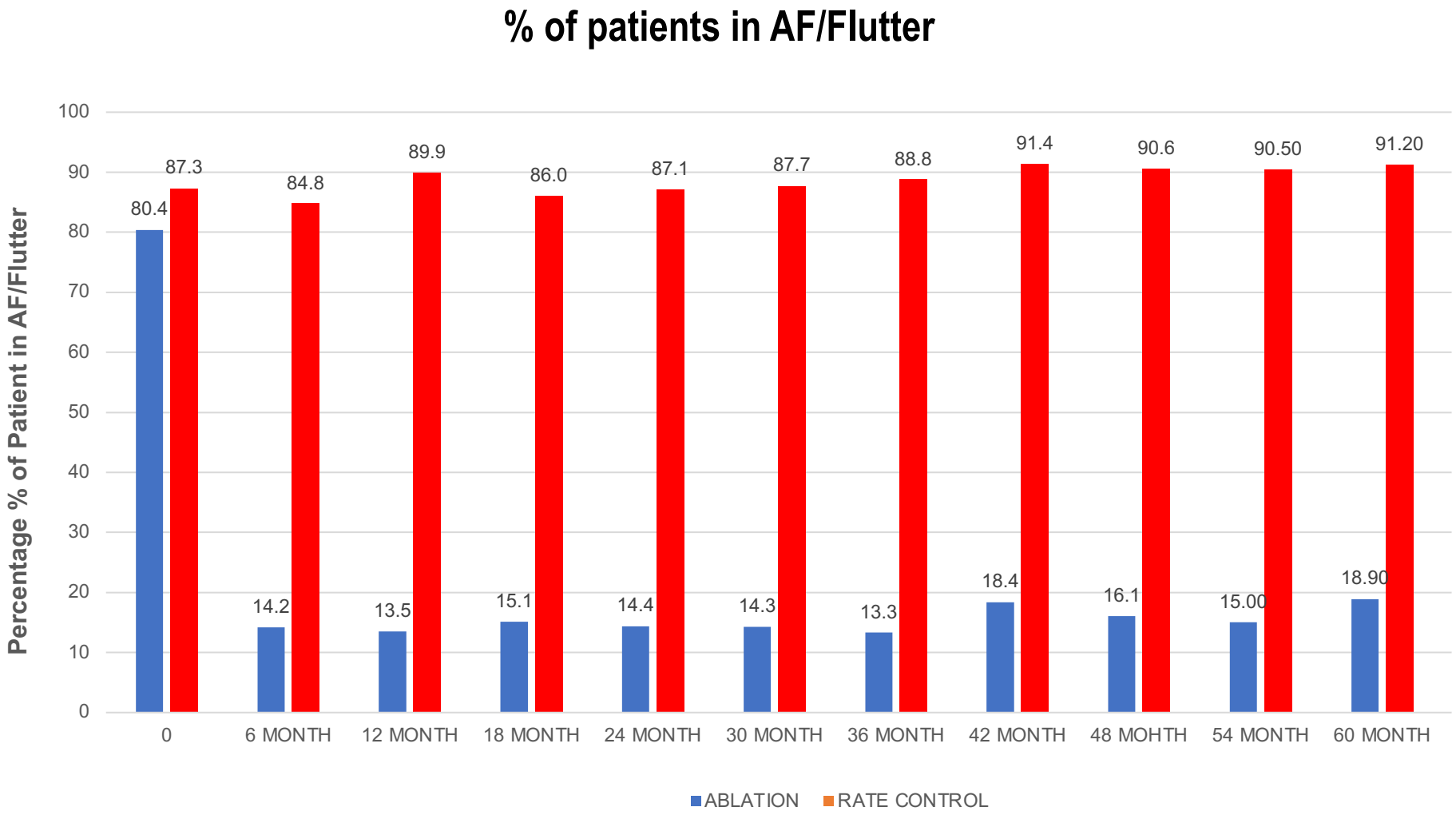
Patients Flow Diagram



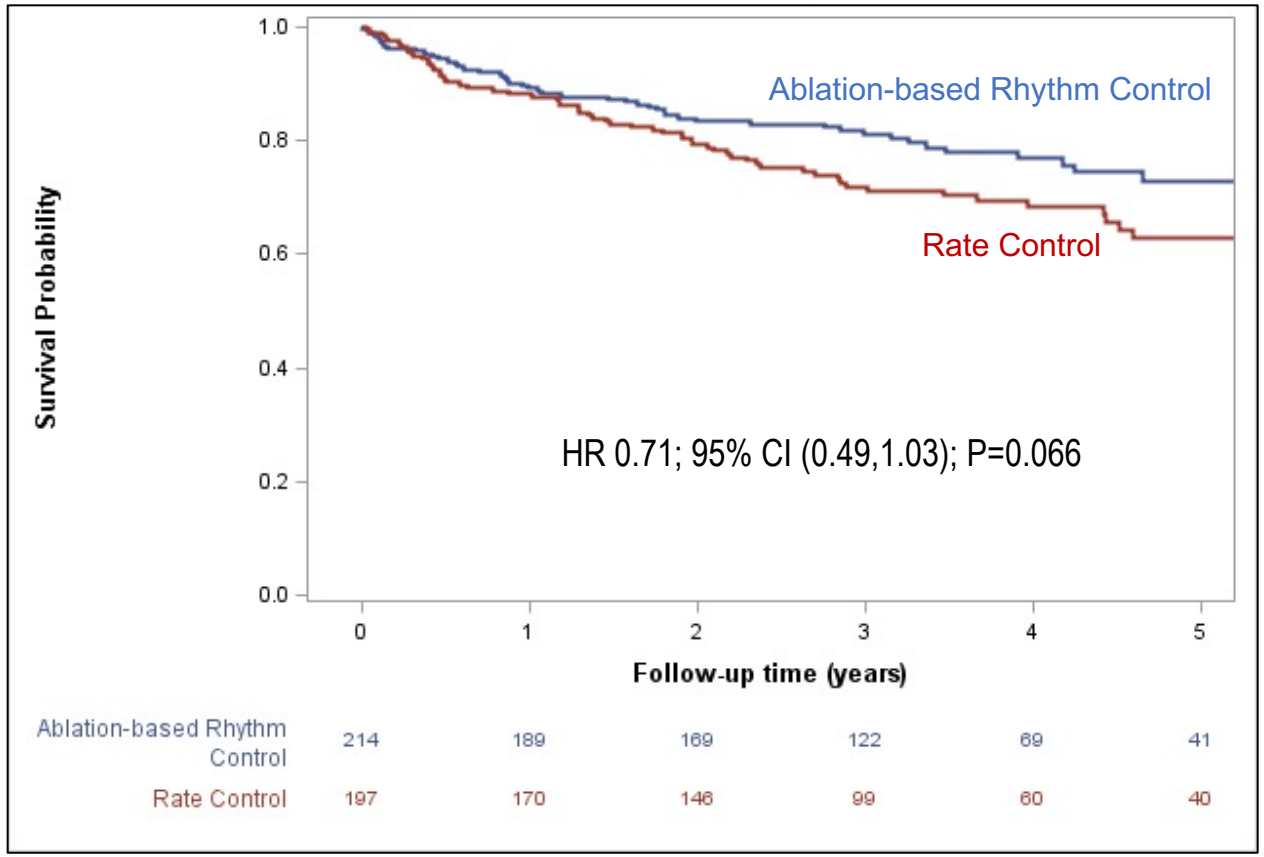
Baseline Patient Characteristics

Characteristic		Rate Control (N=197)	Ablation-based Rhythm Control (N=214)
Age, years (mean±sd)		67.5±8.0	65.9±8.6
Female Sex, N (%)		49 (24.9)	57 (26.6)
BMI (mean±sd)		30.7±6.7	30.1±6.5
Underlying heart disease, N (%).	Ischemic	55 (27.9)	74 (34.6)
	Non-ischemic	142 (72.1)	140 (65.4)
NYHA Class, N (%).	II	131 (66.5)	144 (67.3)
	III	66 (33.5)	70 (32.7)
6 Minute walk distance (mean±sd)		344.4±107.1	363.1±101.4
NT-proBNP (median (Q1,Q3))pg/ml		1583 (1041,2641)	1689 (1000,2743)
Medications, N (%).	Prior or current antiarrhythmic drug	77 (39.1)	94 (43.9)
	Mineralocorticoid receptor antagonist	53 (26.9)	51 (23.8)
	Diuretics oral	140 (71.1)	158 (73.8)
	Beta-blocker	182 (92.4)	197 (92.1)
	Digoxin	65 (33.0)	55 (25.7)
	Calcium Channel Blocker	46 (23.4)	47 (22.0)
	ACEi and/or ARB	161 (81.7)	155 (72.4)
	Anti-coagulant	187 (94.9)	203 (94.9)
Left Atrial diameter, mm (mean ± sd)		46.8±5.4 (n=195)	46.1±6.0 (n=212)
LVEF, 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

Patient's Rhythm in 12 lead ECG at Follow-up



Kaplan-Meier Curves
Primary Outcome – Death and HF Events



Outcomes

	Rate Control N=197	Ablation-based Rhythm Control N=214	Treatment Effect [a]	P value
Primary Outcome	64 (32.5%)	50 (23.4%)	0.71 (0.49,1.03)	0.066
All-cause mortality	34 (17.3%)	29 (13.6%)	0.79 (0.48,1.30)	0.349
Heart failure events	48 (24.4%)	38 (17.8%)	0.71 (0.47,1.09)	0.120
Secondary Outcomes			Effect Size [b]	P value
MLHFQ: change from baseline at 12 months	-13.9±1.7	-20.1±1.6	-5.6 (-9.4, -1.8)	0.0036
at 24 months	-14.8±2.1	-17.4±2.1		
AFEQT: change from baseline at 12 months	16.1±1.6	23.4±1.5	5.9 (2.6, 9.2)	0.0005
at 24 months	18.9±2.0	23.8±1.9		
6-minute walk distance (m) from baseline at 12 months	30.5±7.2	36.4±6.7	22.7 (2.9, 42.5)	0.025
at 24 months	27.5±9.7	44.9±9.1		
NT-pro BNP - % reduction of geometric mean at 12 months	45.4±13.0	80.0±9.6	37.9 (22.1, 51.2)	<0.0001
at 24 months	39.2±11.7	77.1±9.2		
Change in LVEF from baseline at 12 months(%)	4.1±1.0	7.7±0.9	3.2 (0.6, 5.9)	0.017
at 24 months	3.8±1.2	10.1±1.2		

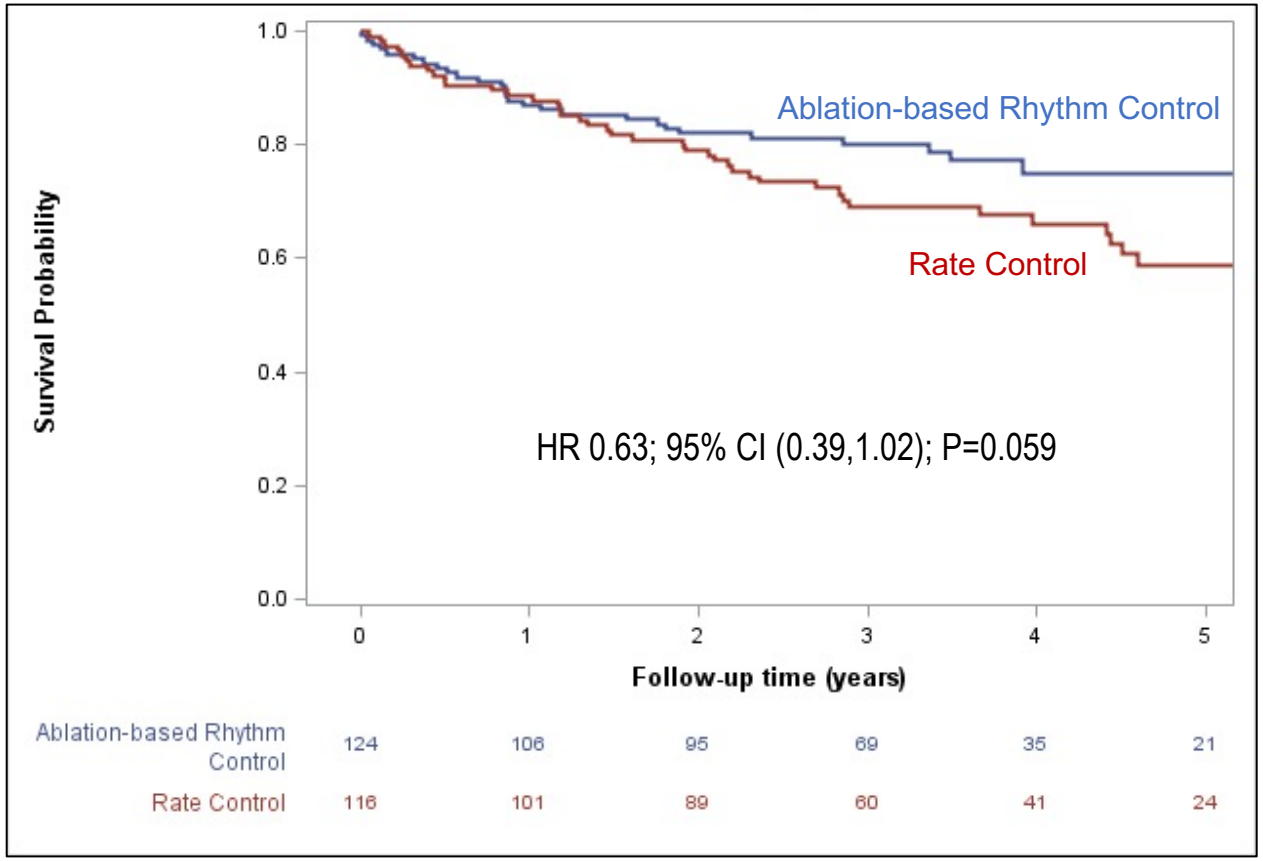
[a] *Treatment Effect is reported as HR (Hazard Ratio) with 95% CI (Confidence Interval)*

[b] *Effect Size with 95% CI determined using the joint model accounting for the competing risk of death*

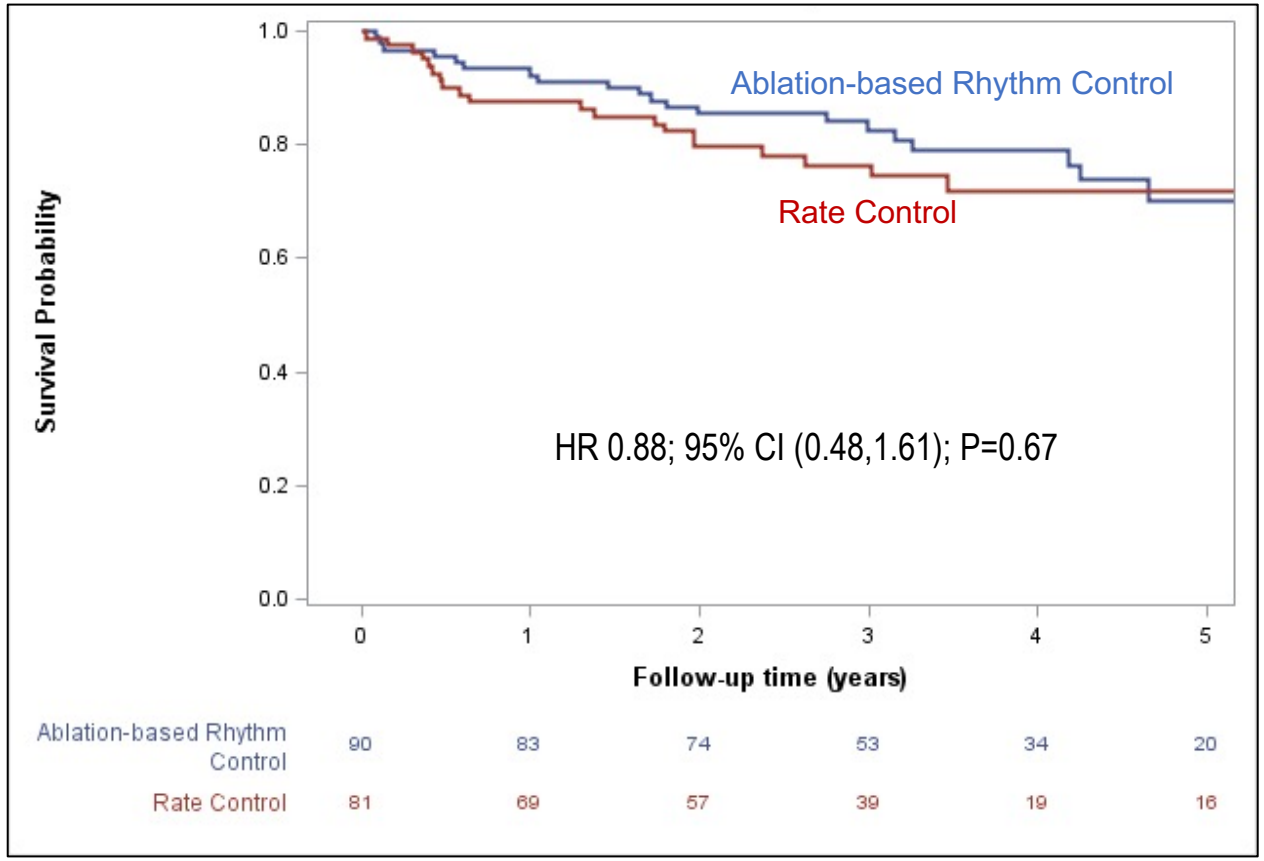
[c] *Changes of Quality-of-Life score, 6-minute walk distance, NT-proBNP and LV ejection fraction at 12, 24 months from baseline are expressed as the least square mean difference (LSMD)±standard error (SE) using a repeated measures linear mixed effects model including group, visit, and group×visit interaction.*

All-cause Mortality and HF Events by LVEF

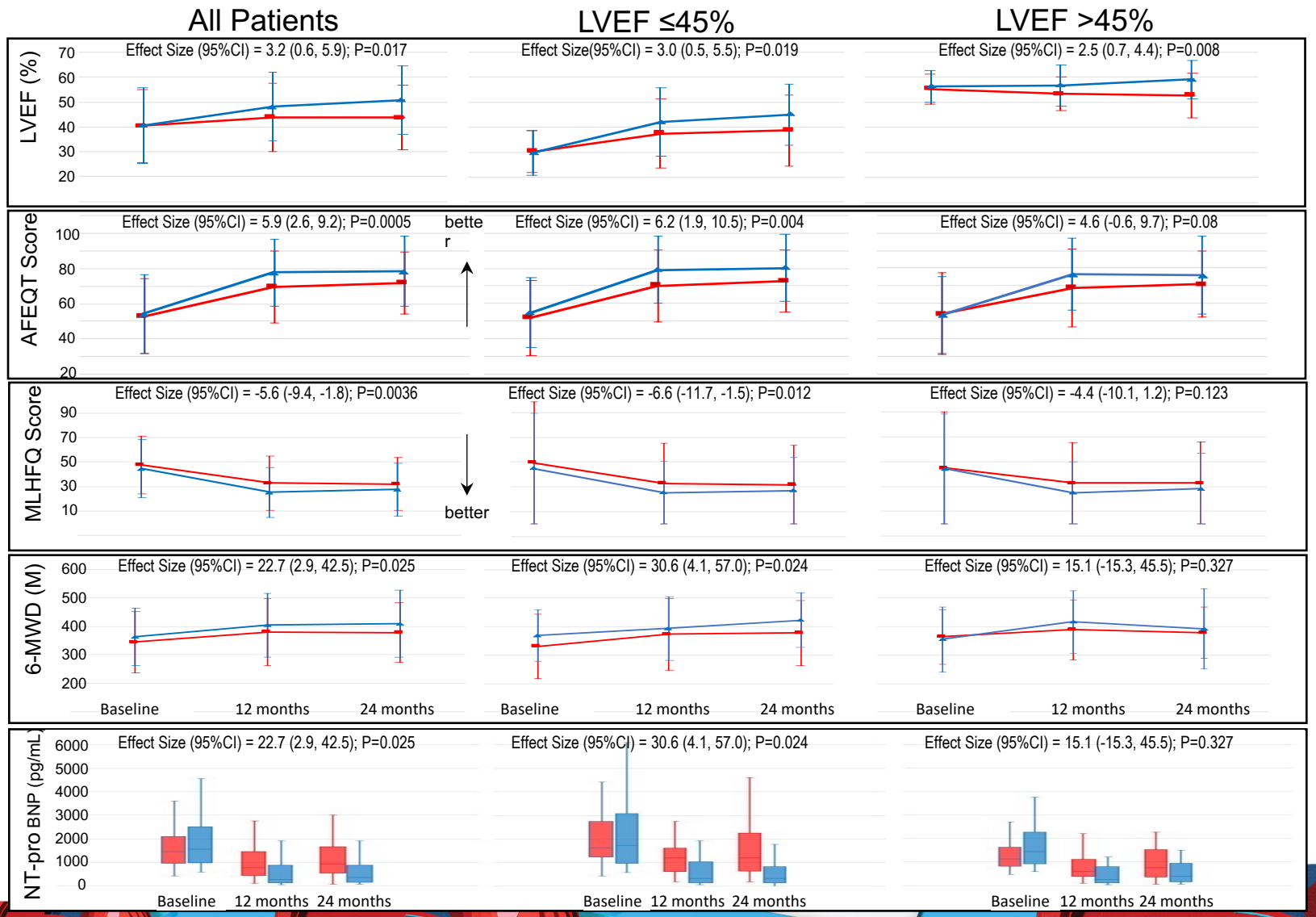
Primary Endpoint in Patient with LVEF ≤45%



Primary Endpoint in Patient with LVEF >45%



Supportive Secondary Outcomes

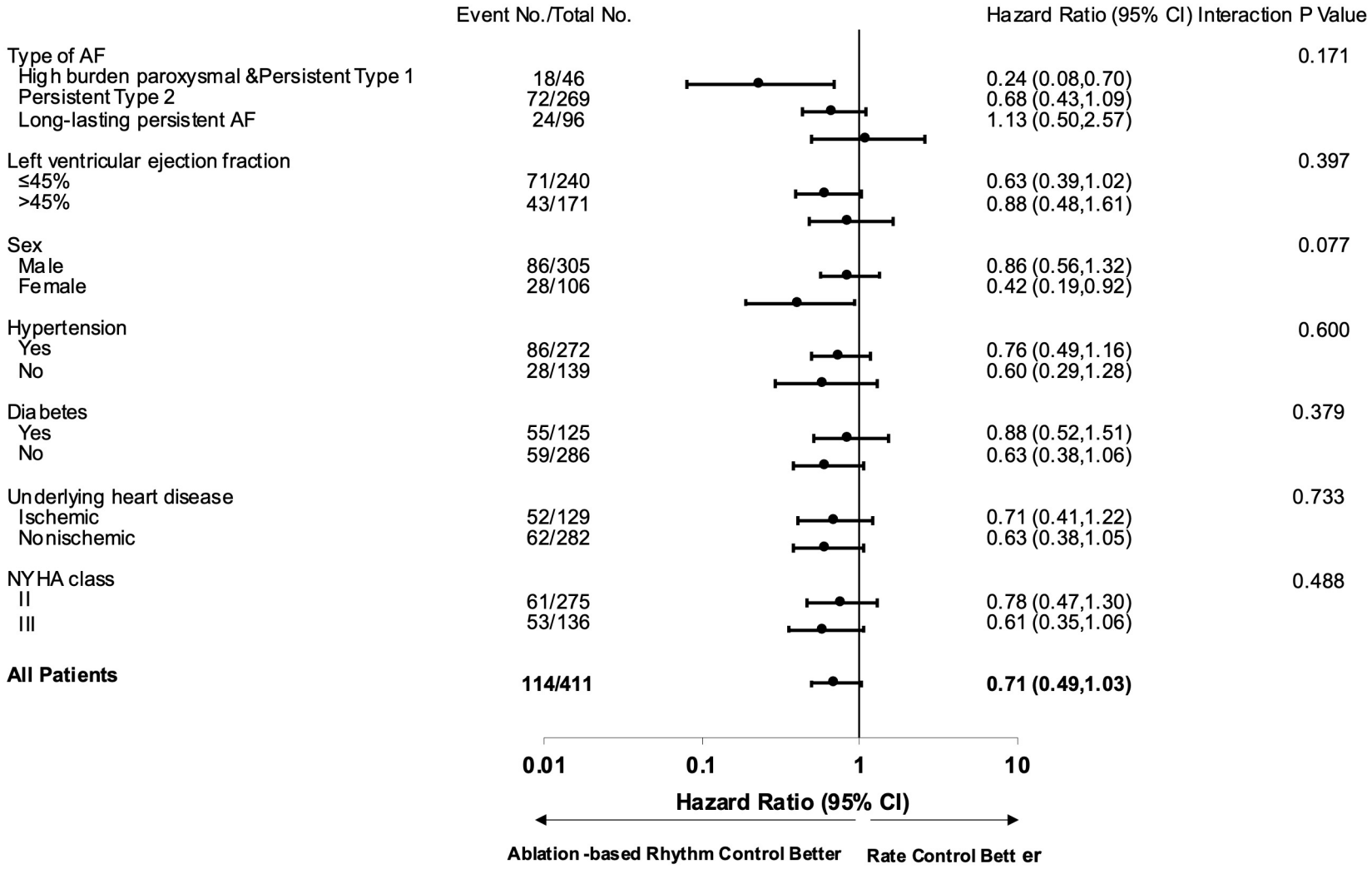


Rate control

Ablation-based rhythm control

Effect size is an estimate of the difference between groups taking into account of time and competing risk of death

Subgroup Analysis



Serious Adverse Events

N (%)	Rate control N=197	Ablation-based rhythm control N=214	P value*
All events	99 (50.3%)	102 (47.7%)	0.5997
Cardiovascular	68 (34.5%)	66 (30.8%)	0.4270
Angina	2 (1.0%)	3 (1.4%)	1.0000
Atrial fibrillation	2 (1.0%)	18 (8.4%)	0.0005
Atrial flutter	1 (0.5%)	8 (3.7%)	0.0384
Heart failure decompensation	48 (24.4%)	38 (17.8%)	0.0999
Myocardial infarction-non-fatal	0	4 (1.9%)	0.1245
Ventricular tachycardia	9 (4.6%)	4 (1.9%)	0.1183
Ventricular fibrillation	2 (1.0%)	0	0.2291
Stroke	5 (2.5%)	5 (2.3%)	1.0000
Transient ischemic attack	2 (1.0%)	0	0.2291
Other CV	13 (6.6%)	9 (4.2%)	0.2815
Non-cardiovascular	56 (28.4%)	57 (26.6%)	0.6846
COPD/pneumonia/asthma	14 (7.1%)	15 (7.0%)	0.9693
Diabetes	1 (0.5%)	0	0.4793
Renal failure	5 (2.5%)	5 (2.3%)	1.0000
Thrombosis	1 (0.5%)	0	0.4793
Other non-cardiovascular	43 (21.8%)	42 (19.6%)	0.5820
Cancer	7 (3.6%)	6 (2.8%)	0.6645
Ablation-related	1 (0.5%)	23 (10.8%)	<0.001
Pseudoaneurysm	0	1 (0.5%)	1.0000
Major bleed per TIMI guidelines	0	8 (3.7%)	0.0077
Iliac dissection	0	1 (0.5%)	1.0000
Minor bleed	0	5 (2.3%)	0.0620
Cardiac perforation, espohageal or pericardial injury	0	9 (4.2%)	0.0038
Other ablation-related (stroke)	1 (0.5%)	4 (1.9%)	0.3741
Device implant/leads/ pulse generator related	4 (2.0%)	1 (0.5%)	0.1986
Other device-related	2 (1.0%)	0	0.2291
Expected battery depletion leading to pulse generate change	1 (0.5%)	0	0.4793
Pocket infection-intervetion	2 (1.0%)	1 (0.5%)	0.6091
AV node ablation related	0	1 (0.5%)	1.0000

Conclusions

- In this trial of patients with AF and HF, the reduction of all-cause mortality and HF events with ablation-based rhythm control did not reach statistical significance as compared to rate control.
- Patients in the ablation-based rhythm control group had numerically fewer primary outcome events, and greater improvement of LV function, improvement of quality of life and reduction of NT-pro BNP than patients in the rate-control group.
- There was no difference in the number of patients with serious adverse events in the two study groups.