SUPPLEMENTAL MATERIAL

Ablation-Based Rhythm Control Versus Rate Control in Heart Failure and High Burden Atrial Fibrillation (RAFT-AF)

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Table S1. RAFT-AF Detailed Inclusion and Exclusion Criteria

Inclusion
Paroxysmal or Persistent atrial fibrillation: a) High burden Paroxysmal defined as ≥4 episodes of atrial fibrillation in the last 6 months, and at least one episode >6 hours (and no other episodes that required cardioversion or was >7 days) b) Persistent atrial fibrillation (Type 1) defined as ≥4 episodes of atrial fibrillation in the last 6 months, and at least one episode >6 hours, and at least one atrial fibrillation episode less than 7 days but requires cardioversion. No atrial fibrillation episodes are >7 days c) Persistent atrial fibrillation (Type 2) as defined by at least one episode of atrial fibrillation >7 days but not >1 year d) Long lasting persistent atrial fibrillation defined as an atrial fibrillation episode, at least one year in length and no episode >3 years
Optimal therapy for heart failure of at least 6 weeks (according to 2009 ACCF/AHA class 1 recommendations).
HF with NYHA class II or III symptoms with either impaired LV function (LVEF ≤45%) as determined by EF assessment within the previous 12 months or preserved LV function (LVEF >45%) as determined by EF assessment within the previous 12 months
An elevated N-terminal pro brain natriuretic peptide (NT-proBNP): Patient has been hospitalized for Heart Failure* in the past 9 months, has been discharged AND: i- Is presently in Normal Sinus Rhythm and NT-pro BNP is ≥400 pg/mL or ii- Is presently in Atrial fibrillation and NT-pro BNP is ≥600 pg/mL **OR** Patient has had no hospitalization for Heart Failure in the past 9 months AND: i- Has had paroxysmal Atrial fibrillation, is presently in Normal Sinus Rhythm and NT-proBNP is ≥600 pg/mL or ii- Is presently in Atrial fibrillation and NT-proBNP is ≥900 pg/mL
Suitable candidate for catheter ablation or rate control therapy for the treatment of atrial fibrillation
Age ≥18
Exclusion criteria
LA dimension >55 mm as determined by an echocardiography within the previous year
Acute coronary syndrome or coronary artery bypass surgery within 12 weeks
Rheumatic heart disease, severe aortic or mitral valvular heart disease using the AHA/ACC guidelines
Congenital heart disease including previous ASD repair, persistent left superior vena cava
Prior surgical or percutaneous atrial fibrillation ablation procedure or atrioventricular nodal (AVN) ablation
A medical condition likely to limit survival to <1 year
New York Heart Association (NYHA) class IV heart failure symptoms
Contraindication to systematic anticoagulation
Renal failure requiring dialysis
atrial fibrillation due to reversible cause e.g. Hyperthyroid state
Are included in other clinical trials that will affect the objectives of this study
History of non-compliance to medical therapy
Unable or unwilling to provide informed consent
Pregnant

Table S2. RAFT-AF Optimal medical therapy

All patients must receive optimal medical therapy for heart failure as per ACC/AHA/HRS guideline for drugs and ICD/CRT
Optimal medical therapy
▪ for impaired (LVEF≤45%) LV function include > 6 weeks treatment with: therapeutic dose of beta-blocker, ACEI or ARB, spironolactone, diuretic
▪ ICD and CRT in appropriate patients according to AHA/ACC guideline
▪ for preserved (LVEF>45%) LV function include: diuretic, beta-blocker

Table S3: RAFT-AF Schedule of follow-up

Evaluation	Screening	BL/ RAND	FUV #1 (2 M)	FUV #2 (4 M)	FUV #3 (6 M & Q6 M)	Exit Visit (End of Study)
Assessment of Eligibility Criteria	X					
Informed Consent	X					
Optimal therapy for HF as per guidelines	X					
Clarification of amiodarone and anti-coagulation status	X					
Demographics	X					
Physical Exam		X	X	X	X	X
Medical & CV History		X				
Medication Assessment		X	X	X	X	X
Blood Chemistry Profile		X			X	X
DICOM ECHO*		X			X (12 M & Annually)*	
12-lead ECG		X	X	X	X	X
NT-proBNP*	X	X			X (12 M & Annually)*	
6 MHW		X	X	X	X	X
QOL questionnaires		X			X	X
14 Day Continuous ECG Monitoring *		X			X* (6 M & Q6M)	

HF, heart failure
CV, cardiovascular
ECHO, echocardiogram
QOL, quality of life

*in a subset of sites

Table S4. RAFT-AF recruitment by site

RAFT-AF Centre	Country	SITE #	RAFT-AF Total Patients randomized
McGill University Health Centre	CA	015	88
London Health Sciences Centre	CA	003	74
Queen Elizabeth II Health Science	CA	006	42
CHUS Le Centre hospitalier universitaire de Sherbrooke	CA	011	33
Libin Cardiovascular Institute of Alberta, Calgary	CA	009	30
Victoria Cardiac Arrhythmia Trials	CA	001	24
Institute de Cardiologie de Montréal	CA	004	17
St. Mary's General Hospital, Kitchener	CA	023	16
Vancouver General/St. Paul's Hospital	CA	013	16
Southlake Regional Health Centre	CA	012	15
Hamilton Health Sciences	CA	007	12
Kingston General Hospital	CA	018	10
University of Ottawa Heart Institute	CA	002	7
Karolinska University Hospital	SWE	021	6
CHUM Centre hospitalier universitaire de Montréal	CA	016	5
Instituto de Cardiologia - FUC RS	BR	020	4
Institut universitaire de cardiologie et de pneumologie de Quebec	CA	008	4
National Taiwan University Hospital	Taiwan	022	3
Toronto General Hospital, UHN	CA	017	2
Sunnybrook Health Sciences Centre	CA	010	2
Royal Alexandra Hospital/U of AB Edmonton	CA	014	1
TOTAL			411

Table S5. RAFT-AF Ablation Procedural details

	Ablation group (n=205)
Time of ablation from randomization (BL) – days (N=205) Mean ± SD	44.7±54.0
Successful pulmonary vein isolation	100%
Patients with one ablation – no. of pts	128 (62.4%)
One repeat procedure – no. of pts	69 (33.7%)
Two repeat procedures – no. of pts	8 (3.9%)
Three repeat procedures- no of pts	0
Time between initial procedure and 1st repeat ablation –Mean ± SD (days)	417.5±336.1
Procedural TIME Mean ± SD (hours)	3.5±1.0
Fluoroscopy time Mean ± SD (minutes)	26.3±28.0
Types of Ablation	
PVI + CFE – no. of pts	40 (19.5%)
PVI+ Mitral LINE	2 (1.0%)
PVI+ Mitral LINE + CFE	5 (2.4%)
PVI+ Roof LINE	69 (33.7%)
PVI+ Roof LINE + CFE	38 (18.5%)
PVI+ Roof LINE + Mitral LINE	10 (4.9%)
PVI+ Roof LINE+ Mitral LINE + CFE	8 (3.9%)
PVI + Posterior box, that will include PVI+roof+posterior lines	9 (4.4%)*
Other types of additional lesions – no. of pts	6(2.9%)**
PVI only	18 (8.8%)

*PVI + Posterior box(n=3), PVI and Roof and Posterior box lesion (n=4), PVI and Roof line and low Posterior line, PVI & Roof line & Posterior wall & CFAE

**PVI & Roof Line & CTI, PVI + Roof line + Floor line (n=3), PVI + Posterior isolation (box) + LA CFE, PVI+CTI,

Table S6. Medication use at last follow-up

Overall	**Rate Control N=147**	**Ablation N=168**
Medications		
Current Anti-arrhythmic Drugs	9 (6.2%)	38 (22.8%)
Mineralocorticoid Receptor Antagonists	44 (29.9%)	53 (31.6%)
Diuretics oral	103 (71.0%)	105 (63.3%)
Insulin	10 (6.9%)	15 (9.0%)
Beta-blocker	129 (89.0%)	124 (74.7%)
Digoxin	33 (22.8%)	11 (6.6%)
Calcium Channel Blocker	40 (27.6%)	24 (14.5%)
Nitrates	8 (5.5%)	4 (2.4%)
Statin	83 (57.2%)	100 (60.2%)
Angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker	116 (78.9%)	110 (65.5%)
Oral hypoglycemics	38 (25.9%)	34 (20.2%)
Oral anticoagulant use	141 (95.9%)	159 (94.6%)
Warfarin	20 (13.6%)	18 (10.7%)
Direct oral anticoagulant	121 (82.3%)	141 (83.9%)
LVEF≤45%	Rate Control N=79	Ablation N=95
Medications		
Current Anti-arrhythmic Drugs	7 (9.1%)	24 (25.3%)
Mineralocorticoid Receptor Antagonists	28 (35.4%)	43 (45.3%)
Diuretics oral	60 (77.9%)	65 (68.4%)
Insulin	7 (9.1%)	8 (8.4%)
Beta-blocker	74 (96.1%)	79 (83.2%)
Digoxin	22 (28.6%)	10 (10.5%)
Calcium Channel Blocker	15 (19.5%)	13 (13.7%)
Nitrates	8 (5.5%)	4 (4.2%)
Statin	44 (57.1%)	60 (63.2%)
Angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker	71 (89.9%)	76 (80.0%)
Oral hypoglycemics	21 (26.6%)	23 (24.2%)
Oral anticoagulant use	76 (96.2%)	90 (94.7%)
Warfarin	11 (13.9%)	12 (12.6%)
Direct oral anticoagulant	65 (82.3%)	78 (82.1%)
LVEF>45%	Rate Control N=68	Ablation N=73
Medications		
Current Anti-arrhythmic Drugs	2 (2.9%)	14 (19.4%)
Mineralocorticoid Receptor Antagonists	16 (23.5%)	10 (13.7%)
Diuretics oral	43 (63.2%)	40 (56.3%)
Insulin	3 (4.4%)	7 (9.9%)
Beta-blocker	55 (80.9%)	45 (63.4%)
Digoxin	11 (16.2%)	1 (1.4%)
Calcium Channel Blocker	25 (36.8%)	11 (15.5%)
Nitrates	2 (2.9%)	0
Statin	39 (57.4%)	40 (56.3%)
Angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker	45 (66.2%)	34 (66.2%)
Oral hypoglycemics	17 (25.0%)	11 (15.1%)
Oral anticoagulant use	65 (95.6%)	69 (94.5%)
Warfarin	9 (13.2%)	6 (8.2%)
Direct oral anticoagulant	56 (82.4%)	63 (86.3%)

Table S7. RAFT-AF Serious Adverse Event Details

N (%)	Rate control	Ablation-based rhythm control	P value*
Classification	**N=197**	**N=214**	
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
Chronic obstructive pulmonary disease /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, esophageal 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
Other AV node ablation related	0	1 (0.5%)	1.0000

*analysis was done on patient-level and patients could have more than one event.

Table S8. Baseline characteristics for LVEF ≤45%

Characteristic	Rate Control	Ablation-based Rhythm Control
	N=116	N=124
Age, years (mean±sd)	67.7±8.1	65.4±9.0
Female Sex, N (%)	22 (19.0)	20 (16.1)
Race, N (%)		
Asian	2 (1.7)	6 (4.8)
Black	0	1 (0.8)
Caucasian/white	113 (97.4)	115 (92.7)
other	1 (0.9)	2 (1.6)
BMI (mean±sd)	30.5±6.5	29.3±6.0
Underlying heart disease, N (%)		
Ischemic	40 (34.5)	56 (45.2)
Non-ischemic	76 (65.5)	68 (54.8)
NYHA Class, N (%)		
II	71 (61.2)	81 (65.3)
III	45 (38.8)	43 (34.7)
Time from first diagnosis of atrial fibrillation (Months, Median (Q1,Q3))	13.5 (6,49)	12 (5,36)
AF type, N (%)		
High burden paroxysmal	6 (5.2)	14 (11.3)
Persistent Type 1: AF<7 days but prior cardioversion	4 (3.5)	3 (2.4)
Persistent Type 2: AF≥7days	79 (68.1)	80 (64.5)
Long-lasting persistent AF ≥ 1 year	27 (23.3)	27 (21.8)
Prior cardioversion, N (%)	62 (53.5)	56 (45.2%)
Cardiac implanted electrical devices (all)	53 (45.7)	55 (44.4)
Implantable cardioverter defibrillator	26 (22.4)	23 (18.6)
Pacemaker	5 (4.3)	6 (4.8)
CRT-P*	0	5 (4.0)
CRT-D*	22 (19.0)	21 (16.9)
Prior Coronary Revascularization (CABG/PCI)† N(%)	33 (28.5)	45 (36.3)
Hospitalization for heart failure in the previous 9 months, N (%)	39 (33.6)	46 (37.1)
CHA_2DS_2-VASc‡ Score, N (%)		
1	14 (12.1)	14 (11.3)
2	18 (15.5)	27 (21.8)
3	29 (25.0)	29 (23.4)
4	24 (20.7)	24 (19.4)
5	21 (18.1)	24 (19.4)
≥6	10 (8.6)	6 (4.8)
6 Minute walk distance (mean±sd)	330.7±113.0	368.7±90.8
NT-proBNP§ (median (Q1,Q3))ρg/ml	1607 (985,2742)	1212 (417,2509)
Medications, N (%)	48 (41.4)	54 (43.6)
Prior or current antiarrhythmic drug	42 (36.2)	46 (37.1)
Mineralocorticoid receptor antagonist	97 (83.6)	104 (83.9)
Diuretics oral	110 (94.8)	114 (91.9)
Beta-blocker	46 (39.7)	39 (31.5)
Digoxin	17 (14.7)	17 (13.7)
Calcium Channel Blocker	67 (57.8)	69 (55.7)
Statin	103 (88.8)	104 (83.9)
Angiotensin converting enzyme inhibitor and/or angiotensin II receptor blocker		
OAC use, total N (%)	108 (93.1)	120 (96.8)
Warfarin	45 (38.8)	37 (29.8)
Direct oral anticoagulant	63 (54.3)	84 (67.7)
Other Comorbidities, N (%)		
Hypertension	79 (68.1)	82 (66.1)
COPD	9 (7.8)	11 (8.9)
Diabetes (DM)	38 (32.8)	40 (32.3)
Stroke/TIA	11 (9.5)	14 (11.3)
Current Tobacco Use, N (%)	5 (4.3)	10 (8.1)
No. of alcoholic drinks per week with>14 for men or >7 for women	7 (6.0)	5 (4.0)
Left Atrial diameter, mm (mean±sd)	47.5±5.5 (n=115)	46.8±6.1 (n=122)

*CRT indicates cardiac resynchronization therapy; P indicates pacemaker; D indicates defibrillator.
†Coronary artery bypass graft surgery/percutaneous coronary intervention
‡ CHA_2DS_2-VASc is a score with one point assigned for each of the following: congestive heart failure, hypertension, age ≥65, age ≥75, diabetes, stroke (two points), vascular disease, female sex
§N-terminal pro brain natriuretic peptide

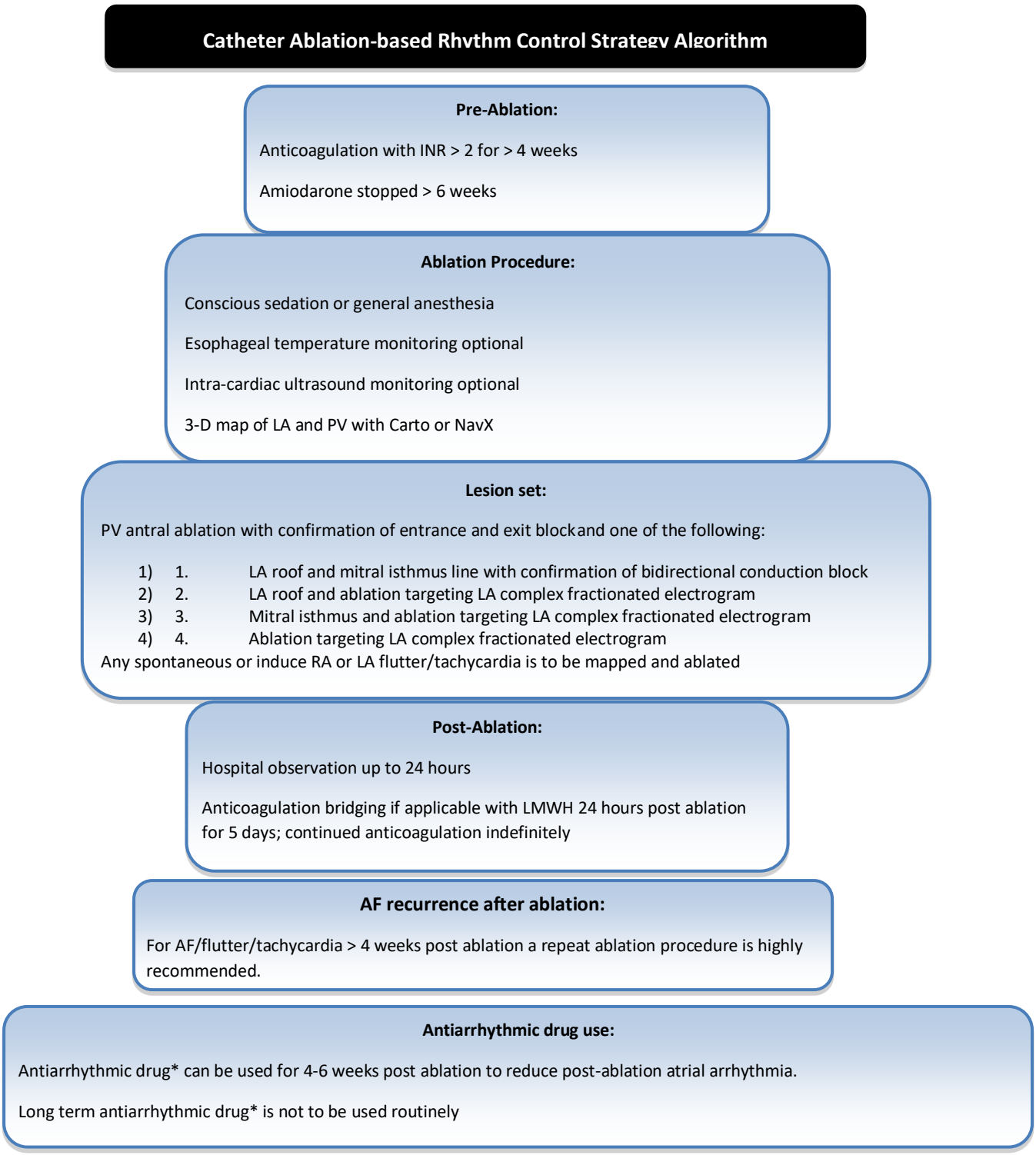
Table S9. Baseline characteristics for LVEF >45%

Characteristic	Rate Control	Ablation-based Rhythm Control
	N=81	N=90
Age, years (mean±sd)	67.2±8.0	66.7±8.0
Female Sex, N (%)	27 (33.3)	37 (41.1)
Race, N (%)		
Asian	1 (1.2)	0
Black	0	1 (1.1)
Caucasian/white	80 (98.8)	89 (98.9)
other	0	0
BMI (mean±sd)	31.1±7.0	31.0±7.1
Underlying heart disease, N (%)		
Ischemic	15 (18.5)	18 (20.0)
Non-ischemic	66 (81.5)	72 (80.0)
NYHA Class, N (%)		
II	60 (74.1)	63 (70.0)
III	21 (25.9)	27 (30.0)
Time from first diagnosis of atrial fibrillation (Months, Median (Q1,Q3))	17 (8,36)	21 (9,36)
AF type, N (%)	5 (6.2)	5 (5.6)
High burden paroxysmal	5 (6.2)	4 (4.4)
Persistent Type 1: AF<7 days but prior cardioversion	50 (61.7)	60 (66.7)
Persistent Type 2: AF≥7days		
Long-lasting persistent AF ≥ 1 year	21 (25.9)	21 (23.3)
Prior cardioversion, N (%)	54 (66.7)	58 (64.4)
Cardiac implanted electrical devices (all)	14 (17.3)	13 (14.4)
Implantable cardioverter defibrillator	1 (1.2)	2 (2.2)
Pacemaker	10 (12.4)	8 (8.9)
CRT-P*	1 (1.2)	2 (2.2)
CRT-D*	2 (2.5)	1 (1.1)
Prior Coronary Revascularization (CABG/PCI)† N(%)	12 (14.8)	19 (21.1)
Hospitalization for heart failure in the previous 9 months, N (%)	21 (25.9)	25 (27.8)
CHA_2DS_2-VASc‡ Score, N (%)		
0	1 (1.2)	1 (1.1)
1	12 (14.8)	11 (12.2)
2	13 (16.1)	20 (22.2)
3	23 (28.4)	24 (26.7)
4	18 (22.2)	20 (22.2)
5	8 (9.9)	12 (13.3)
≥6	6 (7.4)	2 (2.2)
6 Minute walk distance (mean±sd)	364.0±95.4	355.4±114.2
NT-proBNP§ (median (Q1,Q3))ρg/ml	1053 (672,1612)	988 (445,1622.6)
Medications, N (%)	29 (35.8)	40 (44.4)
Prior or current antiarrhythmic drug	11 (13.6)	5 (5.6)
Mineralocorticoid receptor antagonist	43 (53.1)	54 (60.0)
Diuretics oral	72 (88.9)	83 (92.2)
Beta-blocker	19 (23.5)	16 (17.8)
Digoxin	29 (35.8)	30 (33.3)
Calcium Channel Blocker	39 (48.2)	41 (45.6)
Statin	58 (71.6)	51 (56.7)
Angiotensin converting enzyme inhibitor and/or angiotensin II receptor blocker		
OAC use, total N (%)	79 (97.5)	83 (92.2%)
Warfarin	18 (22.2)	18 (20.0)
Direct oral anticoagulant	61 (75.3)	65 (72.2)
Other Comorbidities, N (%)		
Hypertension	53 (65.4)	58 (64.4)
COPD	5 (6.2)	8 (8.9)
Diabetes (DM)	26 (32.1)	21 (23.3)
Stroke/TIA	9 (11.1)	5 (5.6)
Current Tobacco Use, N (%)	7 (8.6)	8 (8.9)
No. of alcoholic drinks per week with>14 for men or >7 for women	7 (8.6)	7 (7.8)

Characteristic	Rate Control	Ablation-based Rhythm Control
	N=81	N=90
Left Atrial diameter, mm (mean±sd)	45.8±5.2 (n=80)	45.2±5.9 (n=90)

*CRT indicates cardiac resynchronization therapy; P indicates pacemaker; D indicates defibrillator.
†Coronary artery bypass graft surgery/percutaneous coronary intervention
‡ CHA_2DS_2-VASc is a score with one point assigned for each of the following: congestive heart failure, hypertension, age ≥65, age ≥75, diabetes, stroke (two points), vascular disease, female sex
§N-terminal pro brain natriuretic peptide

Figure S1. Catheter Ablation-based Rhythm Control Strategy Algorithm



*Antiarrhythmic drugs:

Amiodarone or Dofetilide can be used in patients with impaired LV function; Amiodarone or Dofetilide, can be used in patients with preserved LV function. Amiodarone oral loading 400 mg twice a day or three times a day for 10 days then 200 mg per day. Amiodarone or sotalol could be used in patients with preserved left ventricular function.

Dofetilide 500 mg twice a day when eGFR >60 ml/min; 250 mg twice a day when eGFR is 40-60 ml/min; 125 mg twice a day when eGFR <20 ml/min

ST JUDE VELOCITY CFE MAPPING ALGORITHM

Once in AF, CFE mapping using the automated algorithm will be performed in the LA, CS, and RA (if needed).

EGMs should be obtained during AF by mapping with the circular mapping catheter. In areas where the circular mapping catheter cannot obtain good atrial contact, mapping may be supplemented using the 4 mm tip ablation catheter. Bipolar recordings are to be filtered at 30-300 Hz (default value).

The detailed technique for mapping/ablating CFE using the automated algorithm has been described and validated previously. In brief, the algorithm measures the time between multiple, discrete deflections (-dV/dT) in a local AF electrogram (EGM) recording over a specified length of time (5 sec) and then averages these inter-deflection time intervals to calculate a mean cycle length (CL) of the local EGM during AF. This mean CL is then projected onto the LA anatomical shell as a color-coded display. The shorter the CL, the more rapid and fractionated the local EGM. Specifically for this study, regions with a mean CL of less than 120 ms will be defined as "CFE" based on previously published data[1].

The recommendations and settings for EnSite Complex Fractionated Electrograms Algorithm – CFE is reported in Table 4.

At the start of the procedure, the baseline signal noise level should be determined and the P-P Sensitivity limit is to be set just above the noise level (typically 0.03-0.05 mV) to avoid noise detection while allowing detection of low amplitude CFE (often <0.5 mV).

Selectable peak to peak EGM amplitude, EGM width, and post-EGM refractory period are defined to assist in algorithm deflection detection

Width Value and Refractory Value are typically set at 15-20 ms and 35-45 ms respectively to avoid detection of far-field EGMs and to avoid double-counting individual EGM deflections.

To avoid including signals from bipoles that are internal in the LA, the Interpolation Value of the algorithm should be adjusted (no more than 10 mm) to include only those signals obtained from bipoles with good atrial shell contact. CFE sites defined by the algorithm (CL < 120 ms) will be targeted for ablation. Regions with the shortest CL should be targeted first, followed by longer CL regions (up to 120 ms). Ablation at a CFE site shall be continued until the local EGM is completely eliminated which typically requires 20-60 sec of RF application.

During ablation of CFE sites, the mean atrial fibrillation cycle length (AFCL) and AF regularity should be measured from a selected CS recording. The CS recording with the shortest average CL is recommended, and the same recording should be used for pre- and post-ablation comparisons. AFCL is determined by counting the number of discrete atrial EGMs over a 15 sec recording (x) and dividing 15000 by x. The CS recording should also be examined to look for regularization of AF to atrial flutter or tachycardia during CFE ablation. Termination of AF to a regular atrial rhythm or sinus rhythm during CFE ablation should be recorded. No intravenous antiarrhythmics should be used during CFE ablation to change AFCL or help regularize/terminate AF.

The endpoint for CFE ablation is**:**

Complete elimination of all CFE regions identified by the algorithm in the LA, CS and RA, or

AF termination.

Initially, all CFE sites in the LA and CS should be targeted. If AF does not terminate into sinus or another regularized arrhythmia, CFE in the RA should be mapped and ablated.

If AF still does not terminate, sinus rhythm may be restored by electrical cardioversion

If AF terminates to sinus rhythm, any remaining unablated CFE sites do not need to be ablated.

If AF terminates to an atrial flutter/tachycardia, all remaining CFE sites should be ablated.

If AF terminates to an atrial flutter or tachycardia, and the required randomization ablation strategy has been completed, then the atrial flutter and tachycardia may be ablated or electrically cardioverted at the discretion of the investigator. The location and nature of the additional lesions and/or the cardioversion should be recorded and documented.

Table S10. Recommendations and Settings for EnSite CFE Algorithm

As CFE mapping catheter use the circular mapping catheter or ablation catheter in regions where the circular mapping catheter has poor contact.

The circular mapping catheter is preferable. Its electrodes size and electrodes spacing allow increasing the signal quality.

Assess the baseline noise using the callipers of the DX Landmarking Tools

Parameter	Value	Parameter definition
P-P Sensitivity	0.03-0.05 mV (Just above the baseline noise)	The P-P Sensitivity control is a minimum peak-to-peak voltage required for the detection algorithm to operate. Incoming signals must be larger than the P-P Sensitivity in order to be considered activation by the system.
Width value	15-20 ms	The Width slider controls the minimum complex width to consider for activation. As CFE maps always use -dVdt detection type, this parameter indicates the width of the most negative slope. This setting will avoid detection of far-field smooth deflection.
Refractory value	35-45 ms	The Refractory slider controls the minimum amount of time between detections, in order to avoid over counting a single EGM with multiple components.
EGM Segment Length	min 5 s	The Segment Length indicates the total recording duration at each point.
Interpolation value	4-8 mm	The Interpolation slider controls the minimum distance between surface points necessary for the system to interpolate colour.
Interior Projection Exterior Projection	4-8 mm	Interior and Exterior Projection are projection sliders that control the Maximum/minimum distance that a 3D Point can project to a location on the interior geometry surface. This setting will avoid collection of EGMs from electrodes that are not in good contact with map shell
Auto-colour	ON	The Auto Colour toggle controls whether the system automatically controls the pointers on the colour bar during DX Landmarking. If Auto Colour is enabled, the pointers will adjust to the minimum and maximum data values for all points in the current map.

Set the colour-slider so that the orange-red transition occurs around 120 ms.

All regions < 120 msec will be considered “CFE” region. Those regions will appear red or white.

Confirm accuracy of regions labelled as “CFE” by checking EGMs visually

Target all red-white regions for ablation. This will often require several lesions over “islands” of CFE throughout the atrium. Try to target white spots (the shortest CL) first.

If CFE ablation in the LA and CS do not terminate AF, map and ablate CFE in the RA.

CFAE MAPPING ALGORITHM:
At each mapping site, a 2.5-second window of bipolar EGMs will be analysed online by programmable CFAE Software Module Version 9.7 that provides online automated identification and electroanatomical display of CFE.

The extent and repetitiveness of EGM fractionation are determined by algorithms described in detail elsewhere 28, 30. In brief, a programmable lower threshold for EGM identification is set to exclude noise (±0.05 mV). Voltage peaks greater than this threshold but less than an upper threshold (±0.15 mV) is then identified.

The intervals between successive peaks falling within the voltage window and within a programmable duration (60–120 ms) are then counted and summed over the 2.5 second sampling window, designated the interval confidence level (ICL). ICL can be depicted as a color-coded gradient map on the LA and CS shells (fill threshold 10 mm). All sites with higher ICL (>7) reflect more repetitive CFE and will ultimately be targeted for generalized CFAE ablation.

TIPS AND TRICKS FOR CFAE and CFR MODULES IN CARTO:

It is important to understand that automated modules are meant to assist the operator in identifying areas of interest. However, like any automated tool, the information provided must be verified and calibrated before each case.

In the CFAE module, there is a voltage range which specifies a lower limit (default = 0.03 mV) and an upper range (0.15 mV). This means that no signals below 0.03 mV will be annotated (to avoid noise detection) and no signal above 0.15 mV will be annotated (since CFAE are supposed to be low voltage signals). However, the lower limit may need to be adjusted depending on the noise level of your lab. As a check, you can place the ablation catheter in the middle of the LA (no wall contact). Measure the voltage on the recording. Ideally, it should be zero (in a noiseless lab), but if it is above 0.03 mV, you may need to increase the lower limit so as to filter out this noise. The upper limit is typically fine as is, however, if you have a "young, healthy" atrium, where the voltages are very high throughout, even the CFAE can have a higher voltage. Thus, you may need to increase the upper voltage limit (up to 0.30 mV) in order to accommodate this.

In the CFAE module, there is also a minimum (default 50 ms) and a maximum (default 100 ms) duration identified for the intervals. Remember, the ICL is the number of short intervals between successive low-amplitude deflections. The more the number of short intervals, the more "fractionated" the signal. Any interval less than 50 ms will not be identified as a unique interval (to avoid double-counting a single electrogram) and no interval greater than 100 ms will be identified as a unique interval (to avoid long, isoelectric pauses between signals). In the paper by Wilber et al, JCE 2008, the default values set were a lower limit of 60 ms and an upper limit of 120 ms. For most cases, these settings do not make a tremendous difference. However, in patients who start off with a longer cycle length AF (almost a cross between AF and AFL or "flitter"), the upper limit may need to be extended beyond 100 ms (up to 150 ms).

Here's how you can easily determine where the most optimal settings should be:

1. First place your catheter in the middle of the LA (no wall contact) to measure the noise level and adjust the lower voltage limit accordingly

2. Quickly look at the voltages of the signals in the LA. If they are very robust, you may need to adjust the upper voltage limit

3. Quickly look at the cycle length of the AF. If it is more of a "flutter" with a cycle length >190 ms, then you may need to adjust the upper duration limit

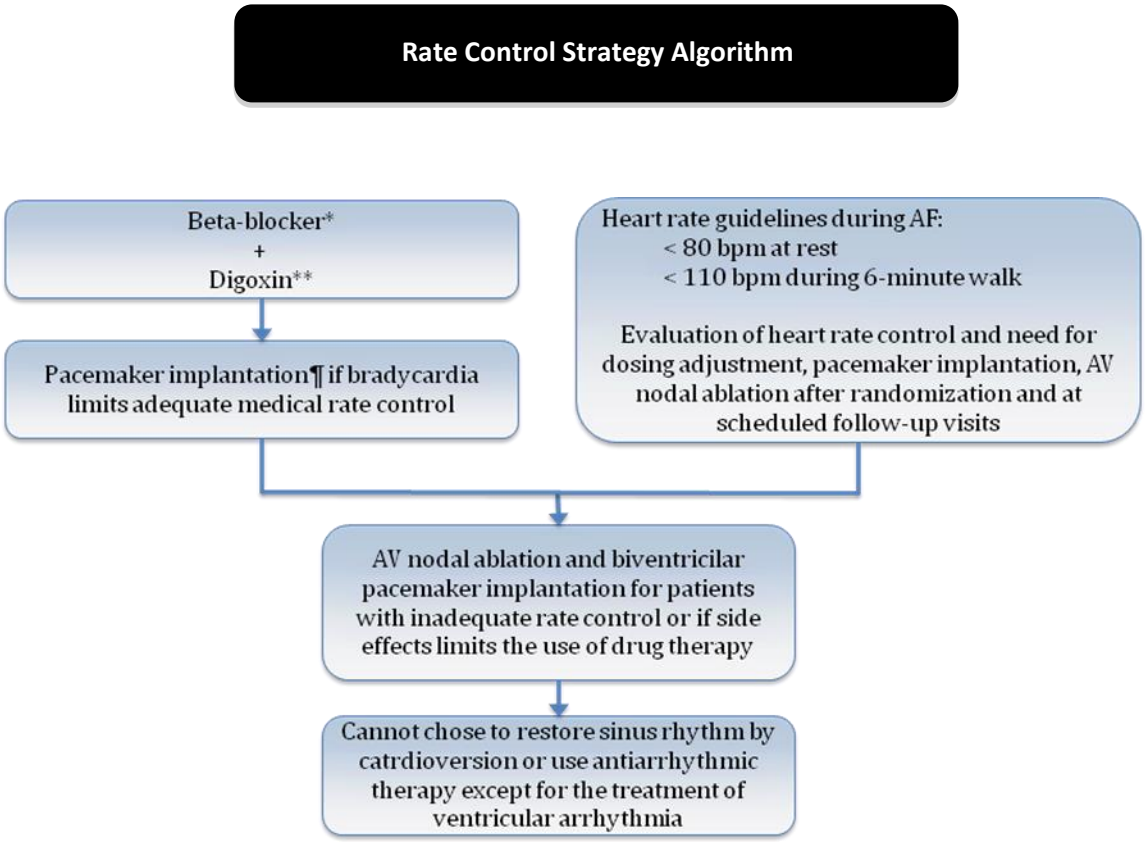
4. To decide how much to adjust the voltage and duration limits, place your catheter in a position where you obviously have CFAE or continuous fractionation by visual inspection. Acquire a point. If it gives you a value that seems to correlate with your visual inspection, then the algorithm is working well. If not, then adjust the limits until the value is in line with what you are seeing. Think of this as a calibration test.

The other issue that comes up is the amount of LA that is identified as CFAE:

1. The whole LA has been labelled as CFAE. What do I do?

First, check that your ICL limit has been established at 7 (not 5). Second, do your calibration check as outlined in the last section. If everything seems to be working OK, then perhaps your atrium does have a lot of CFAE. Here's how I handle this - adjust your ICL limit to 9 or 10 to highlight only those VERY fractionated regions. Start ablating only these areas. AF may terminate as a result of this. If not, then gradually extend your ablation lesions by lowering the ICL limit towards 7.

Figure S2. RAFT-AF Rate control strategy algorithm



* Beta-blocker: Metoprolol - starting 6.25 mg - 25 mg twice a day, maximum 50 - 100 mg twice a day.

Carvedilol - starting 3.125 mg twice a day, maximum 25 -50 mg twice a day.

Bisoprolol – starting 1.25 mg/day, maximum 10 mg/day.

** Digoxin: 0.125 to 0.25 mg/day according to age, renal function and concomitant medication.

¶Pacemaker: Recommend biventricular pacemaker when AV nodal ablation is to be used to control heart rate.

ICD and CRT: Recommend in the case of impaired LV function as per ACC/AHA guidelines

Figure S3. Kaplan-Meier Distribution of Mortality by Treatment Group

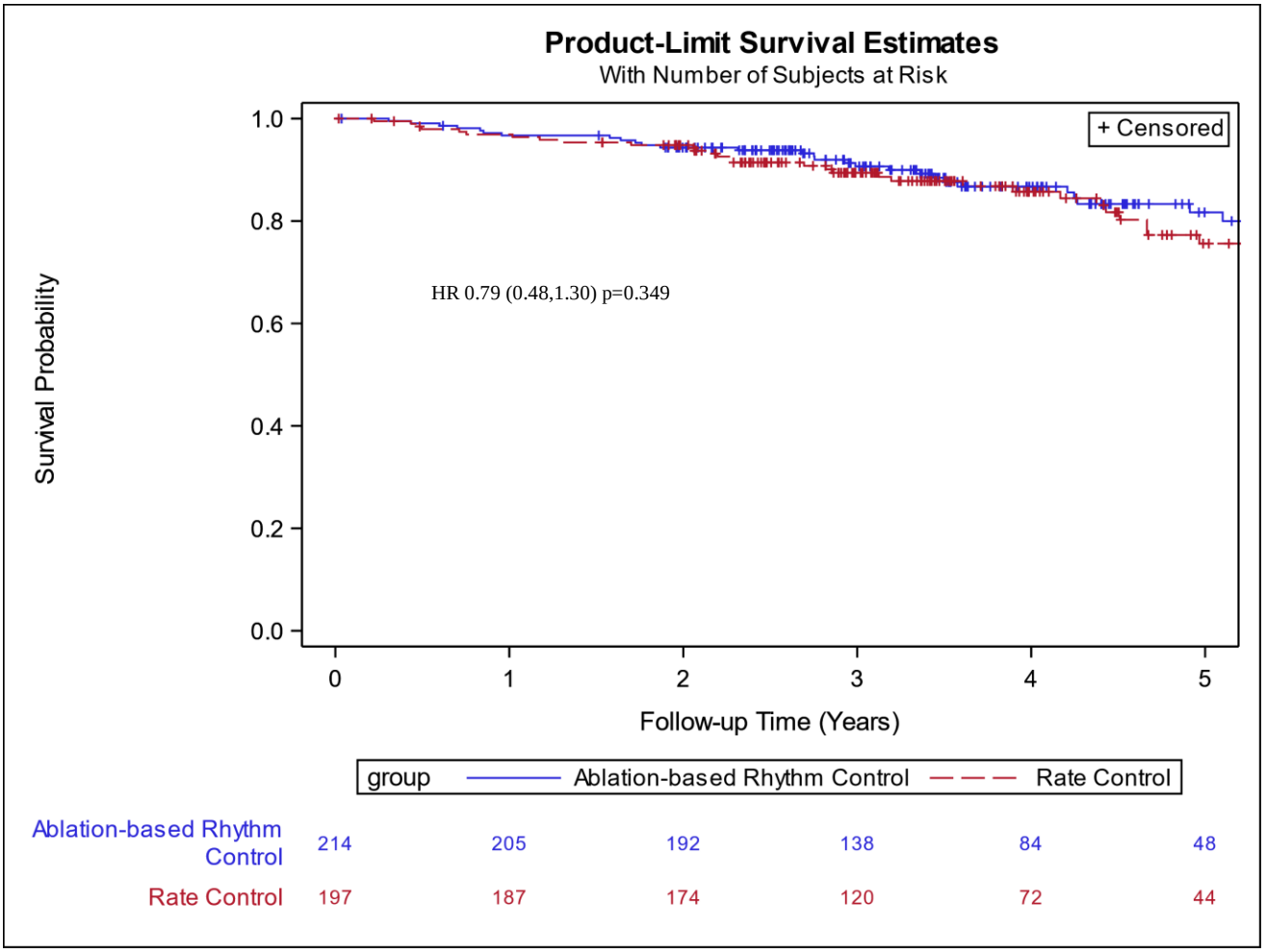


Figure S4. Cumulative Incidence of Heart Failure Events by Group

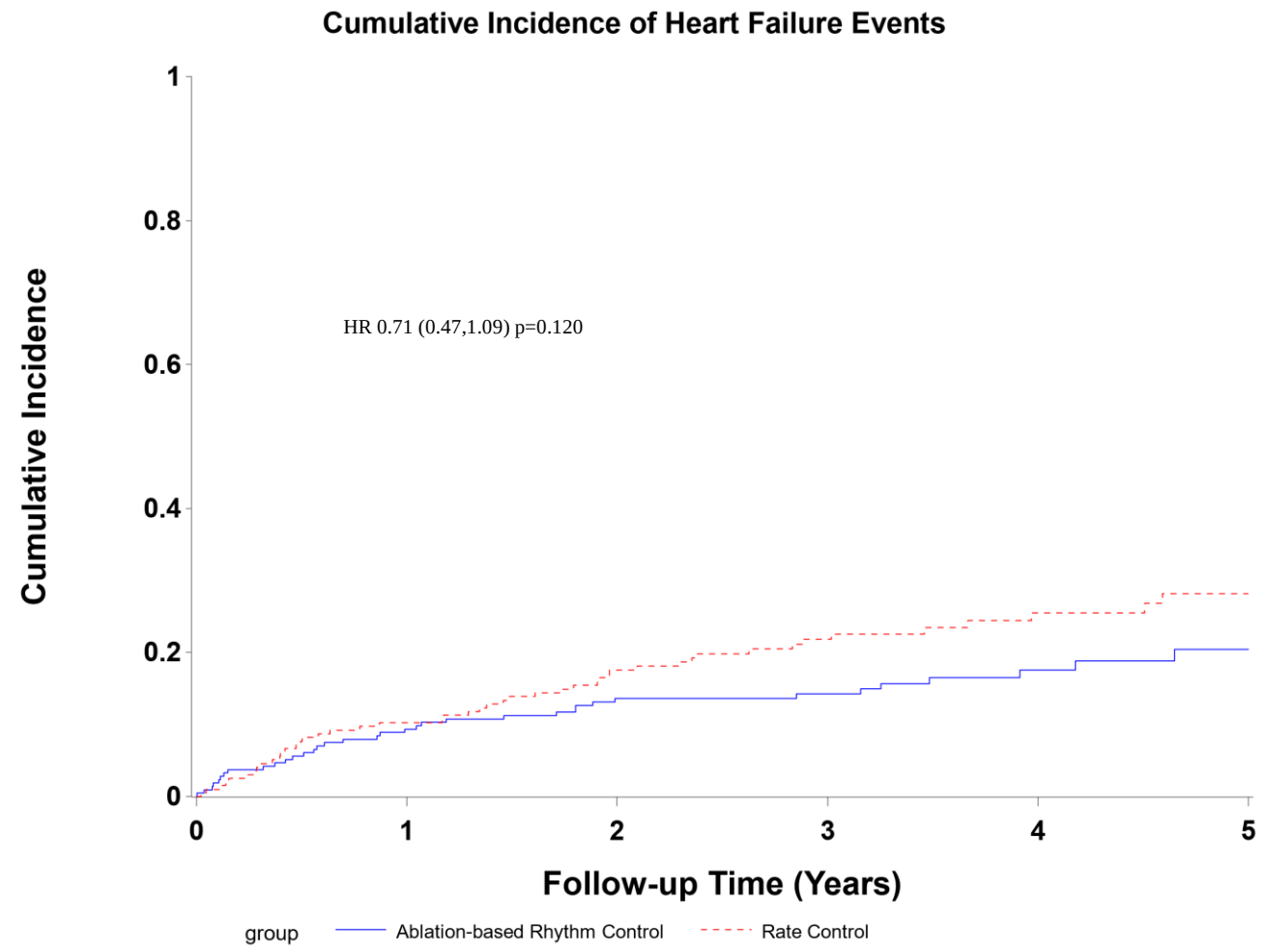


Figure S5. RAFT-AF Left Ventricular Ejection Fraction at 12 and 24 months by Treatment Strategy

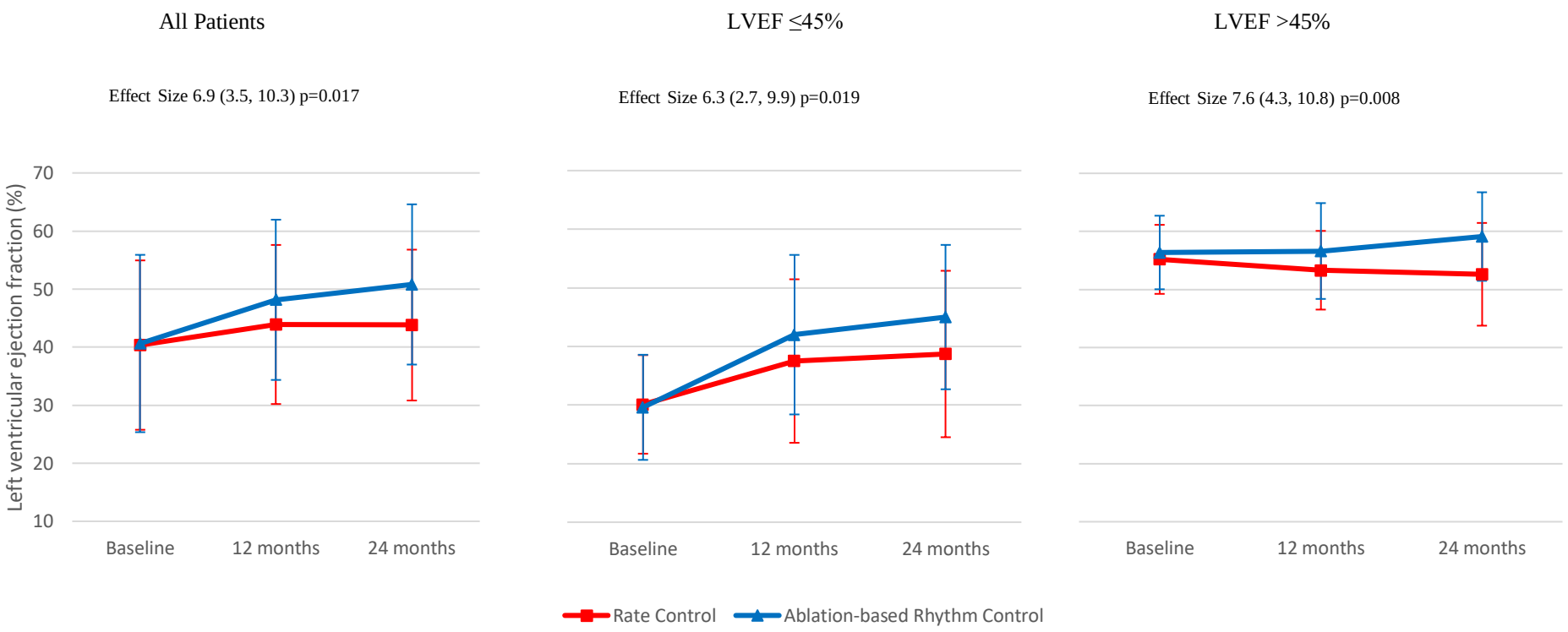


Figure S6a. RAFT-AF AFEQT Questionnaire at 12 and 24 months by Treatment Strategy

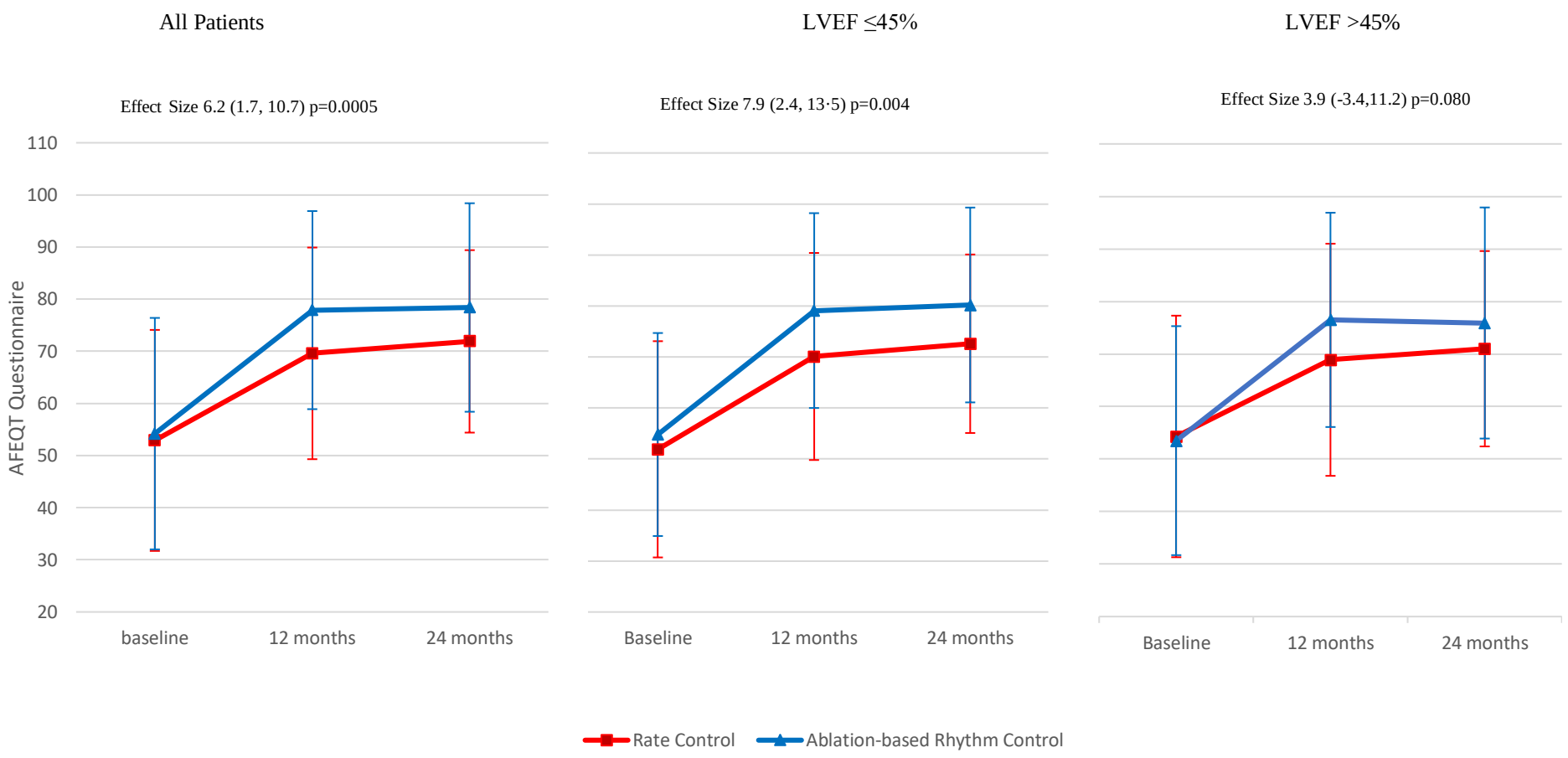


Figure S6b. RAFT-AF MLWHF Questionnaire at 12 and 24 months by Treatment Strategy

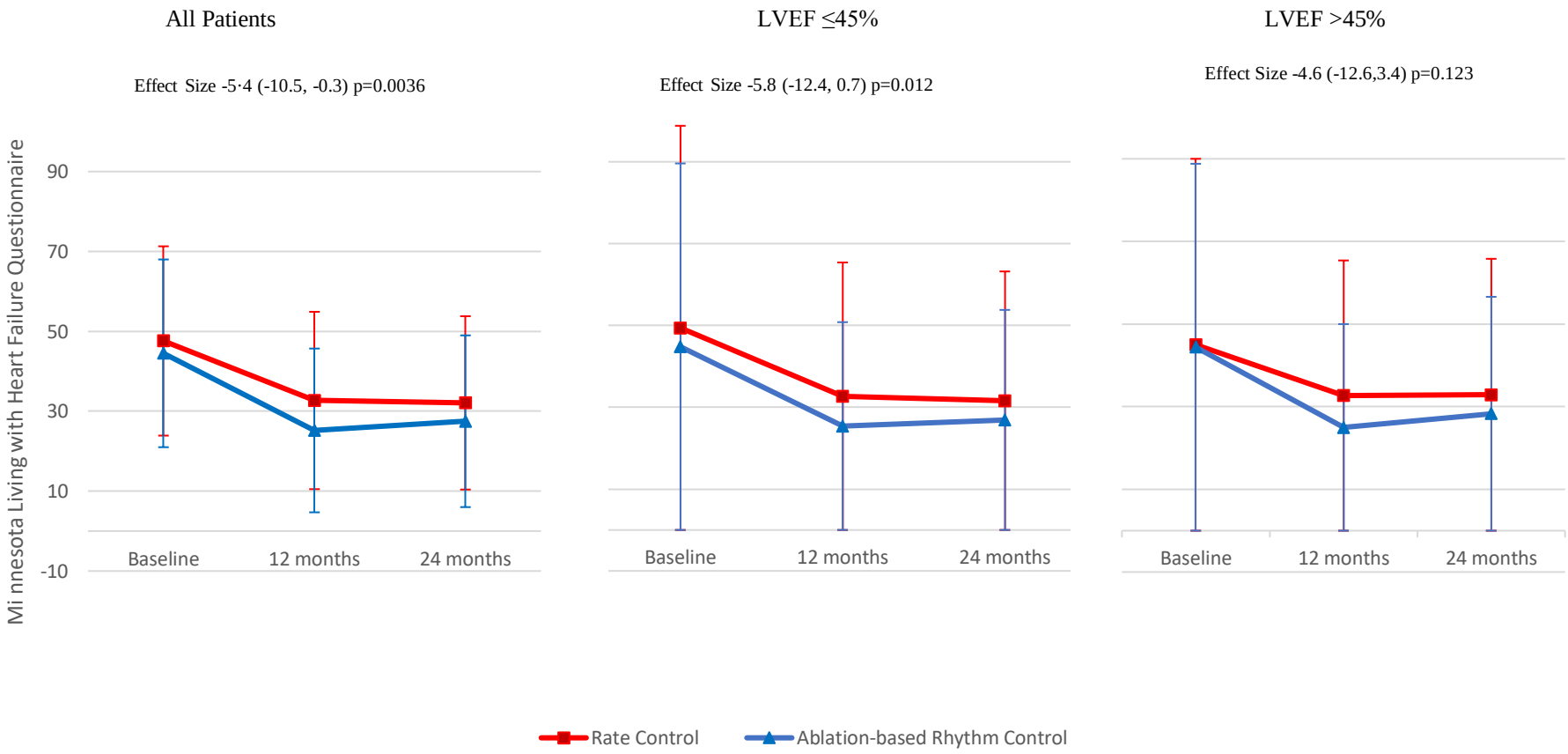


Figure S7. RAFT-AF Six minute walk test at 12 and 24 months by Treatment Strategy

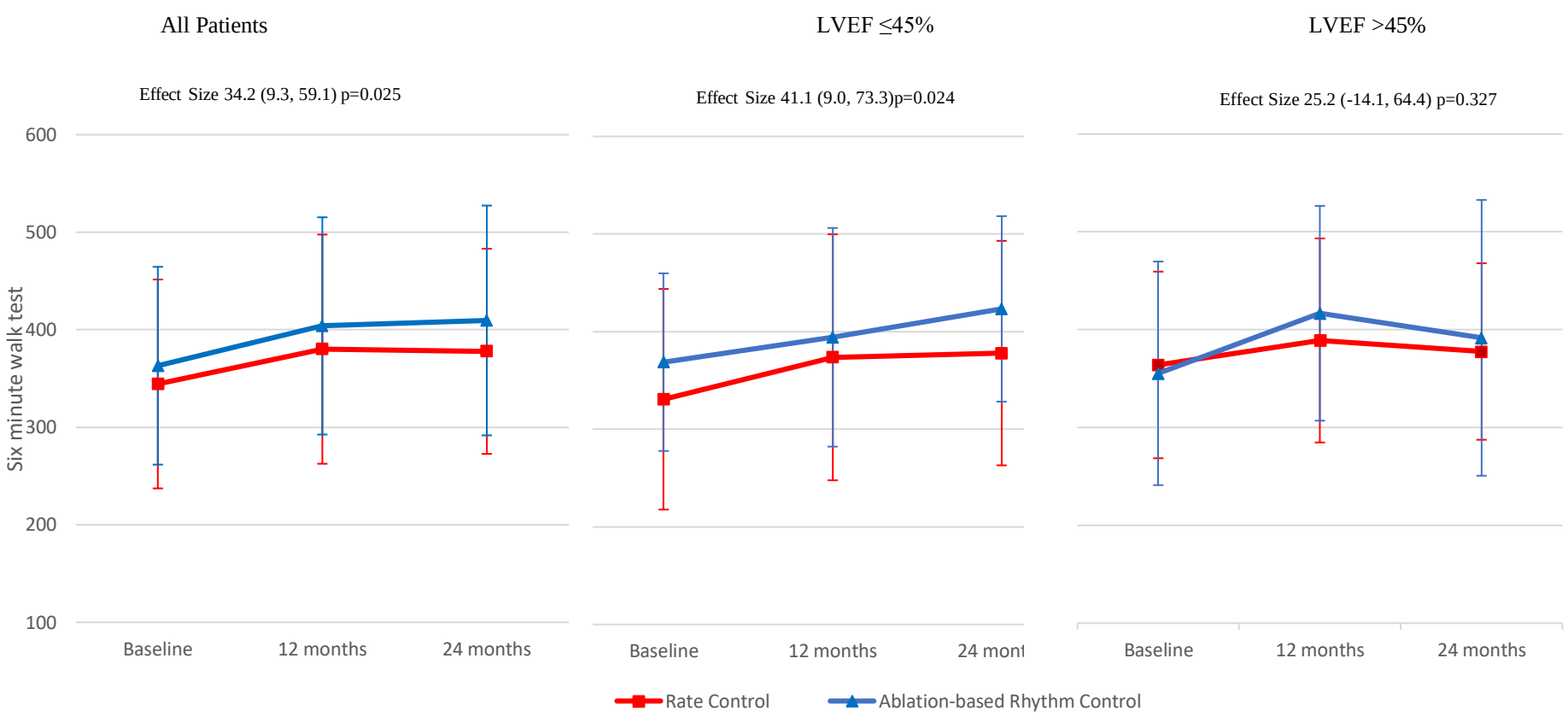


Figure S8. RAFT-AF NT-proBNP at 12 and 24 months by Treatment Strategy

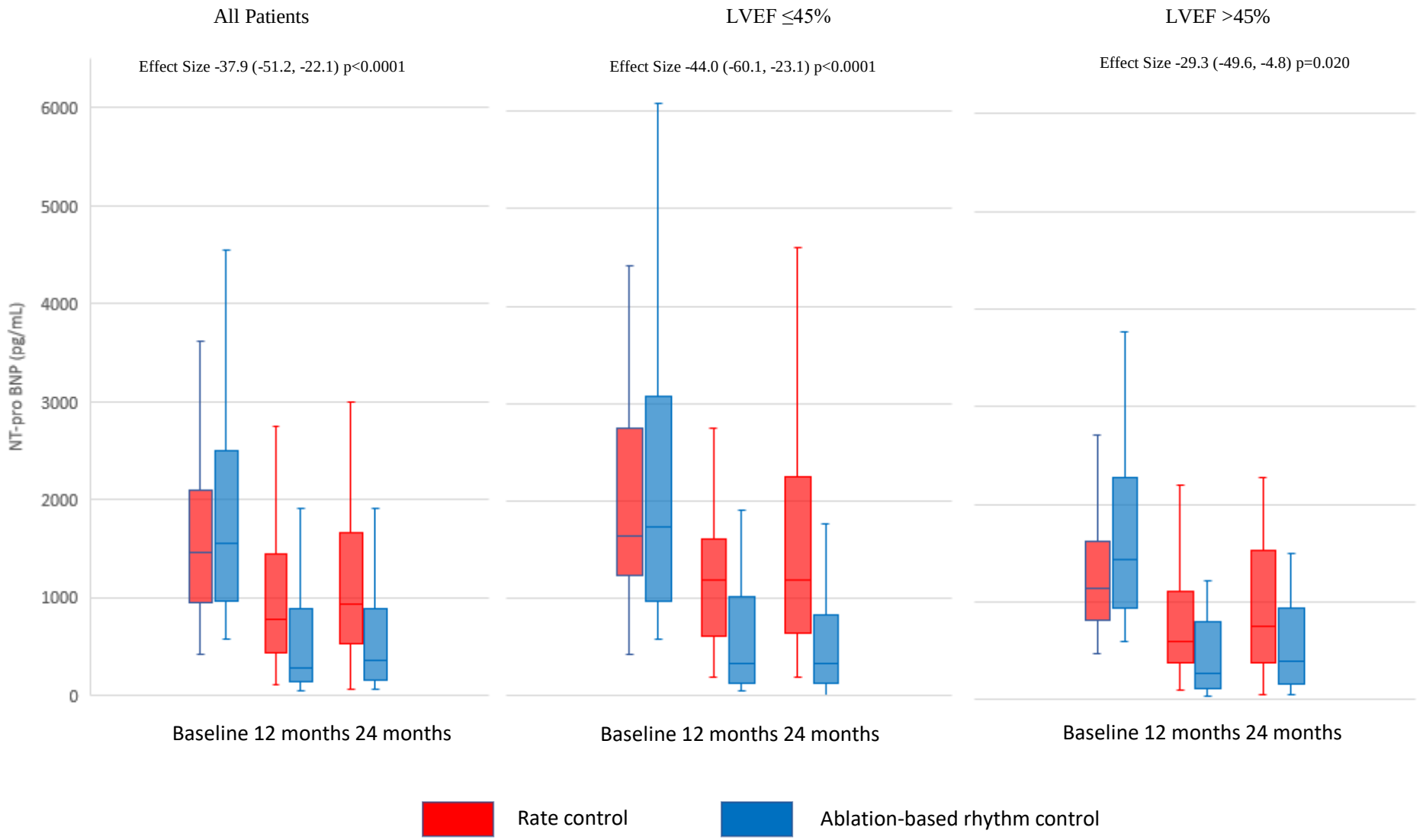


Figure S9. Ghosh–Lin curve: Cumulative recurrent heart failure events

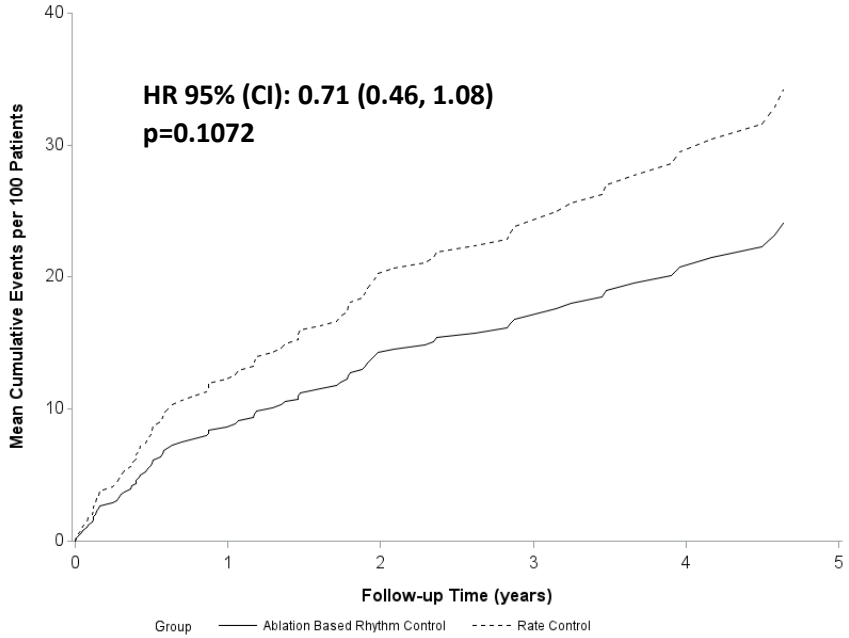
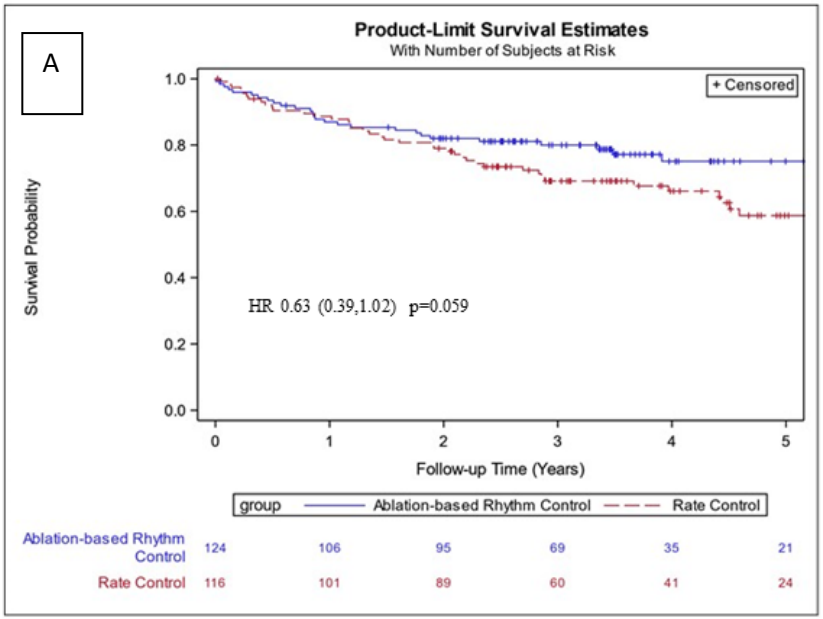


Figure S10. Freedom from All-cause Mortality or Heart Failure Event by LVEF group.

Panel A represents LVEF ≤45%; Panel B represents LVEF >45%.



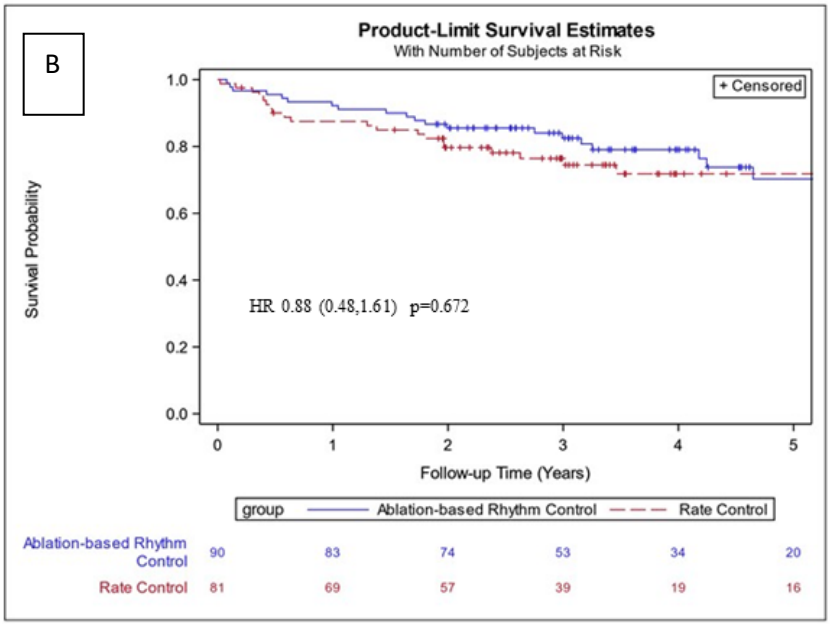


TABLE S11. DSMC DATA SEPTEMBER 2017

MORE INFORMATIVE 'STATUS OF THE EXPERIMENT' REPORT ('MISER')

Trial Name: **RAFT-AF**		
PICOT Question: Among the patients with HF (either impaired or preserved LV function) and high burden AF, does the catheter ablation-based AF rhythm control, compared to rate control, reduce all-cause mortality and hospitalizations for heart failure defined as an admission to a health care facility for >24 hours, over a minimal follow-up of 2 years?		
Protocol Plan vs. Results at this DMC Meeting: (Data on**: 9 Sep 2017**)		
PATIENT STATUS	Protocol Plan	Current Performance
Randomized: Ablation (A)	300	191
Randomized: Rate Control (R)	300	172
Median Follow-Up Months (Q1,Q3)	36	A: 20.2 (10.3,38.2) R: 19.6 (9.8,40.9)
EFFICACY	Protocol Plan	Current Performance
Primary Composite Outcome (Unrefuted)		
Ablation Arm	11.9%	30 (15.7%)
Rate Control Arm	17%	22 (12.8%)
Hazard Ratio (95% CI)	0.70	1.32 (0.76,2.28)
Other pre-specified outcomes, sub-groups or secondary analyses? ❍No ●Yes		
Are Statistical Warning Rules due for application at this time? ❍No ●Yes		

OTHER EFFICACY OUTCOMES		
Secondary Outcome (Unrefuted)	Ablation Arm	Rate Control Arm
All-cause Mortality	17 (8.9%)	12 (7.0%)
CV Mortality	11 (5.8%)	8 (4.7%)
All-cause Hospitalization	61 (31.9%)	37 (21.5%)
HF Hospitalization	20 (10.5%)	16 (9.3%)
CV Hospitalization	40 (20.9%)	28 (16.3%)
Subgroups (Unrefuted)	Ablation Arm	Rate Control Arm

Impaired (LVEF≤45%)		
Primary Composite Outcome	19 (17.0%)	17 (15.9%)
Preserved (LVEF>45%)		
Primary Composite Outcome	11 (13.9%)	5 (7.7%)
Paroxysmal AF		
Primary Composite Outcome	1 (5.6%)	4 (36.4%)
Persistent AF		
Primary Composite Outcome	29 (16.8%)	18 (11.2%)

Appendix

List of RAFT-AF Participating Centres: Investigators, Co-Investigators, Research Coordinators

Canada

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Taiwan

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RAFT-AF Steering Committee: Dr. Anthony Tang, Dr. George Wells, Dr. Mario Talajic, Dr. Jean Rouleau, Dr. Ratika Parkash, Dr. Atul Verma, Dr. Vidal Essebag, Dr. David Birnie, Dr. Jeff Healey, Dr. Laurent Macle, Dr. Gary Newton, Dr. Doug Coyle, Dr. Allan Skanes, Dr. Stephen B. Wilton

RAFT-AF Data Safety and Monitoring Board: Dr. George Wyse (Chair), Dr. Dennis Cassidy, Dr. Lehana Thabane

RAFT-AF Ablation Committee: Dr. Atul Verma, Dr. Carlos Morillo

RAFT-AF Event Committee: Dr. Jeff Healey (Co-Chair), Dr. Gary Newton (Co-Chair), Dr. John Sapp, Dr. Francois Philippon, Dr. Lorne Gula, Dr. Elizabeth Swiggum, Dr. Lisa Mielniczuk, Dr. Pablo Nery, Dr. Isabelle Nault, Dr. Stephen B. Wilton, Dr. Andrew Ha, Dr. Lena Rivard, Dr. TIago Luiz Luz Leiria, Dr. Stanley Tung

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RAFT-AF Detect AF Core Lab: Dr. Ratika Parkash (Chair), Anita MacDonald, Marcia Shields