

The FIRE AND ICE Trial

Cryoballoon or Radiofrequency Ablation for
Paroxysmal Atrial Fibrillation

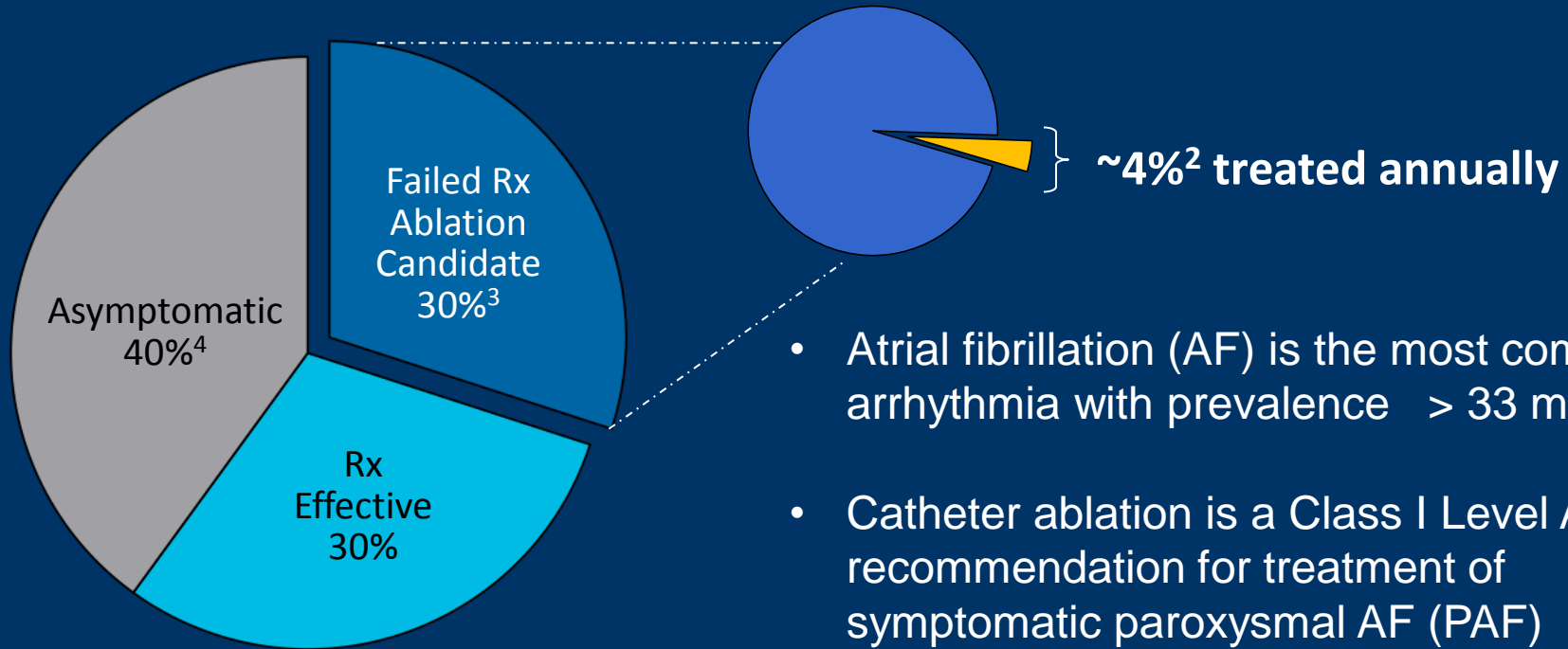
Primary Endpoint and Secondary Analyses Results

(ClinicalTrials.gov NCT01490814)

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Background



- Atrial fibrillation (AF) is the most common arrhythmia with prevalence > 33 million¹
- Catheter ablation is a Class I Level A recommendation for treatment of symptomatic paroxysmal AF (PAF) refractory or intolerant to ≥ 1 Class I or III antiarrhythmic drug (AAD)⁵
- Pulmonary vein isolation (PVI) is the cornerstone of AF ablation strategy⁶

1. Rahman, et al. Nat. Rev. Cardiol. 2014; 11: 639–654

2. Medtronic internal estimates taking into account of clinical and economic exclusion

3. Wyse, et al. Circ. 1996; 93:1262-1277

4. Savelieva, et al. Pace. 2000; 23: 145-148

5. Calkins, H., et al. Heart Rhythm. 2012; 9(4): p. 632-696.e20

6. Raviele et al. J Cardiovasc Electrophysiol, 2012;23:890-923

Objectives and Hypothesis

- Compare the safety and efficacy of PVI by either:
 - **Cryoablation** (Arctic Front™ / Arctic Front Advance™ catheters) guided by fluoroscopy OR
 - **RFC ablation** (THERMOCOOL® / THERMOCOOL® SF / THERMOCOOL® SMARTTOUCH® catheters) guided by CARTO® 3D mapping system
- Primary Efficacy Endpoint: Time to first documented recurrence of AF>30s/AT/AFL, prescription of AAD, or re-ablation
Analysis Methods: Non-inferiority log-rank test
 - Assumed event-free 1 year survival rates of 70% with 10% non-inferiority margin corresponding to HR=1.43
- Primary Safety Endpoint: Time to first all-cause death, all-cause stroke/TIA or treatment-related serious AEs (e.g. phrenic nerve injury, atrioesophageal fistula, etc.)

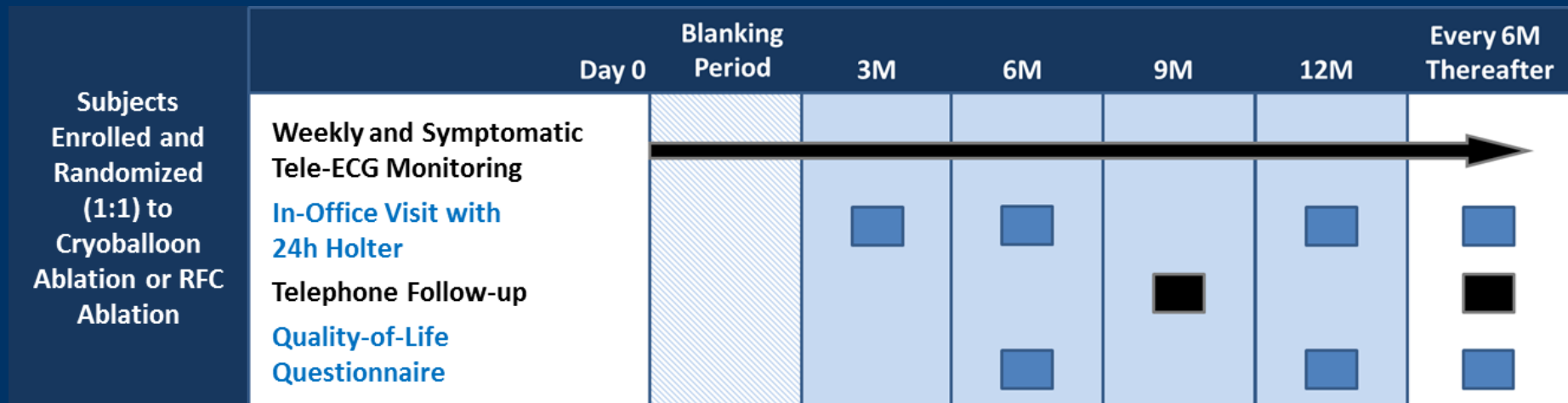
Methods

Key Inclusion Criteria

- Symptomatic PAF
- Prior AAD failure
- ≥ 18 & ≤ 75 years of age

Key Exclusion Criteria

- Previous LA ablation or surgery
- PCI, MI within 3M of enrollment
- Stroke/TIA within 6M of enrollment
- LVEF < 35%
- LA diameter > 55mm



Maximum follow-up duration of 33 months

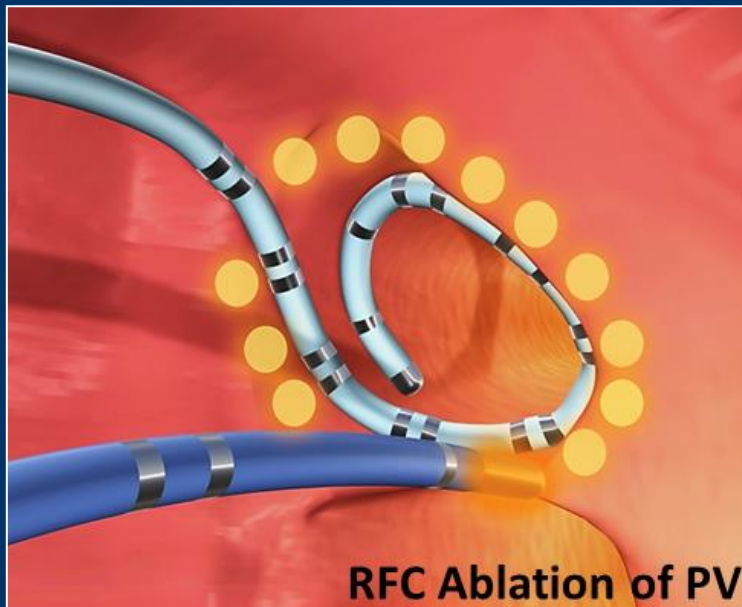
Methods

- Investigators must have documented experience
 - ≥ 50 cases with either technology; each center had to provide at least one investigator proficient in both techniques
 - ≥ 10 cases before introduction of advanced-generation catheters
- Anticoagulation per guidelines/hospital standards
- PVI-only approach (CTI flutter ablation allowed, no additional lines or CFAE ablation)
- Must confirm PV isolation with a mapping catheter
 - 30-minute waiting period after last application
- Energy source crossover not permitted
- AADs discontinued after 90 day blanking period
 - Amiodarone required to be discontinued day of procedure

Methods

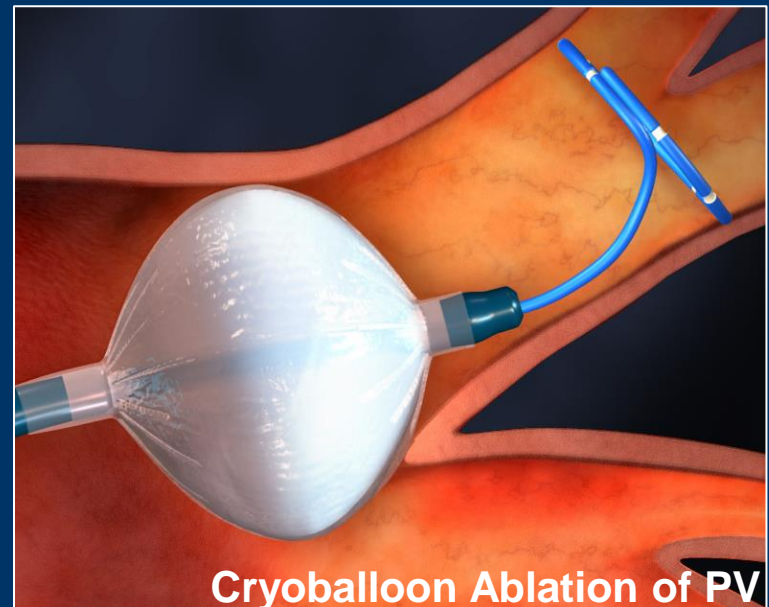
RFC Ablation (“FIRE”)

- Power was not to exceed
 - 40 Watts at A/I aspect
 - 30 Watts at P/S aspect
- 3D electroanatomical mapping

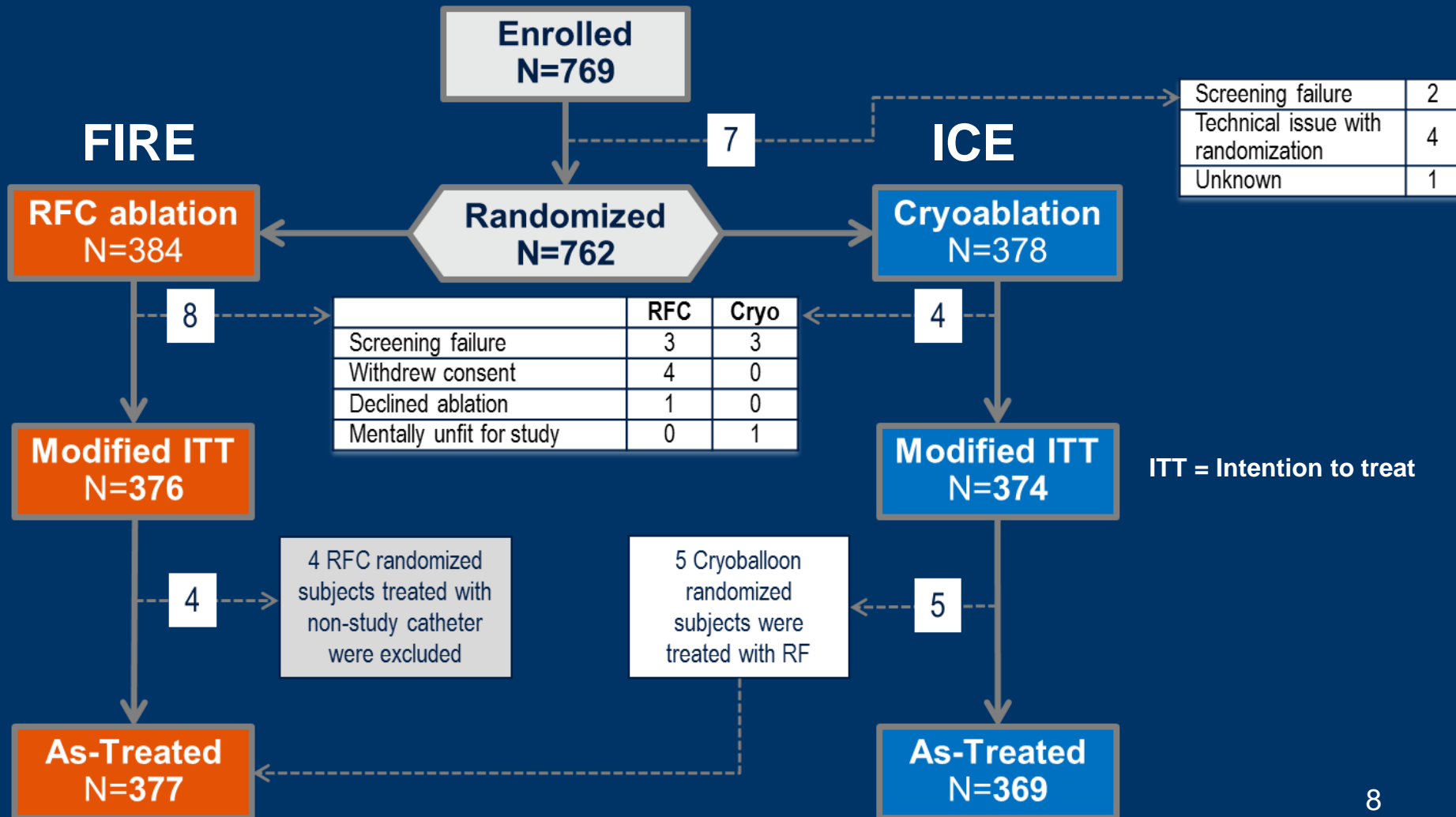


Cryoballoon Ablation (“ICE”)

- Max. freeze duration of 240s recommended
- Bonus freeze after isolation recommended
- Phrenic nerve pacing required



Patient Flow Chart



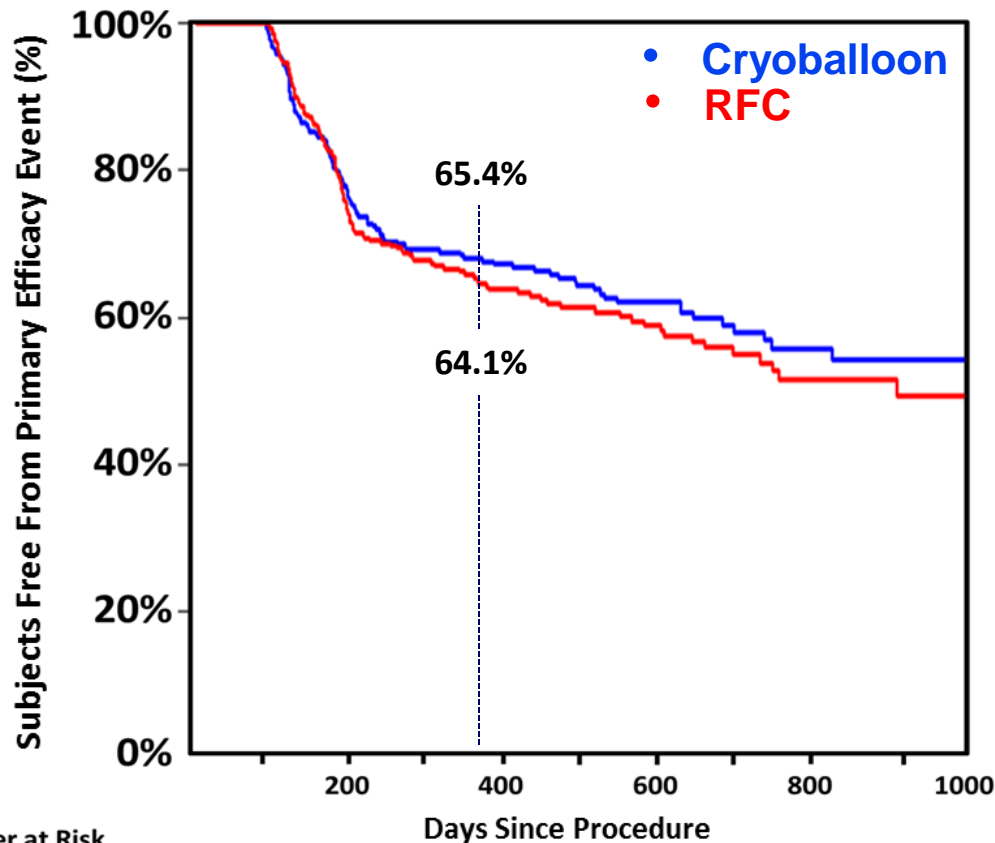
Patient Demographics and Follow-up

	RFC (n=376)	Cryoballoon (n=374)	P- value*
Age, years	60.1 ± 9.2	59.9 ± 9.8	0.83
Men, n (%)	236 (63)	221 (59)	0.30
BMI, kg/m ²	27.8 ± 4.5	28.0 ± 4.7	0.66
CHA ₂ DS ₂ -VASc Score, n (%)			0.19**
0	67 (17.8)	58 (15.5)	
1	109 (29.0)	108 (28.9)	
2	97 (25.8)	95 (25.4)	
3	62 (16.5)	60 (16.0)	
4	33 (8.8)	40 (10.7)	
5	7 (1.9)	10 (2.7)	
6	1 (0.3)	3 (0.8)	
Years Since First PAF Diagnosis	4.7 ± 5.3	4.6 ± 5.1	0.97
Left Atrial Diameter, mm	40.6 ± 5.8	40.8 ± 6.5	0.58
Previous DC Cardioversion	23.4%	23%	0.89
Systolic Blood Pressure, mm Hg	134.8 ± 18.9	133.6 ± 18.0	0.40
Diastolic Blood Pressure, mm Hg	78.9 ± 10.6	78.8 ± 11.5	0.83

Patient Follow-up		
	RFC (n=376)	Cryoballoon (n=374)
Visits	2007 / 2372 (85%)	2006 / 2317 (87%)
Mean F/U Time	1.54 ± 0.79 years	1.54 ± 0.80 years
Total F/U Time	577 patient years	576 patient years
Weekly Tele- ECG	60.0%	58.1%

Primary Endpoint Results

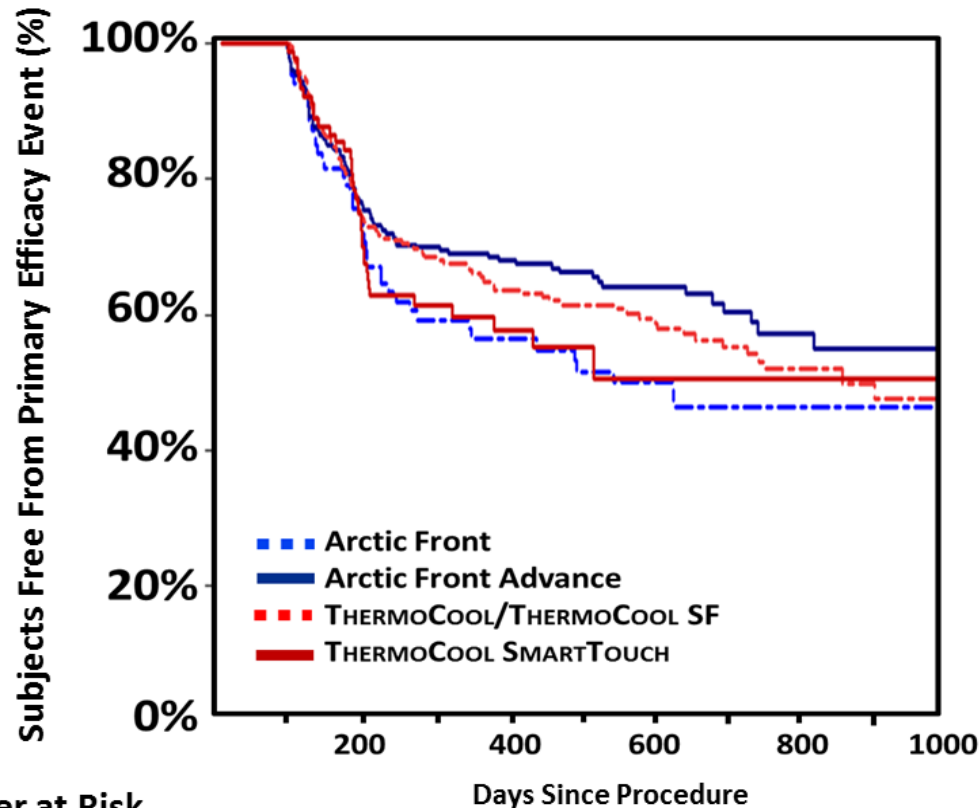
Primary Efficacy Endpoint Met



Modified ITT analysis

- Non-inferiority hypothesis met
- HR [95% CI] = 0.96 [0.76-1.22]; $p = 0.0004$
- Superiority test: $p = 0.74$

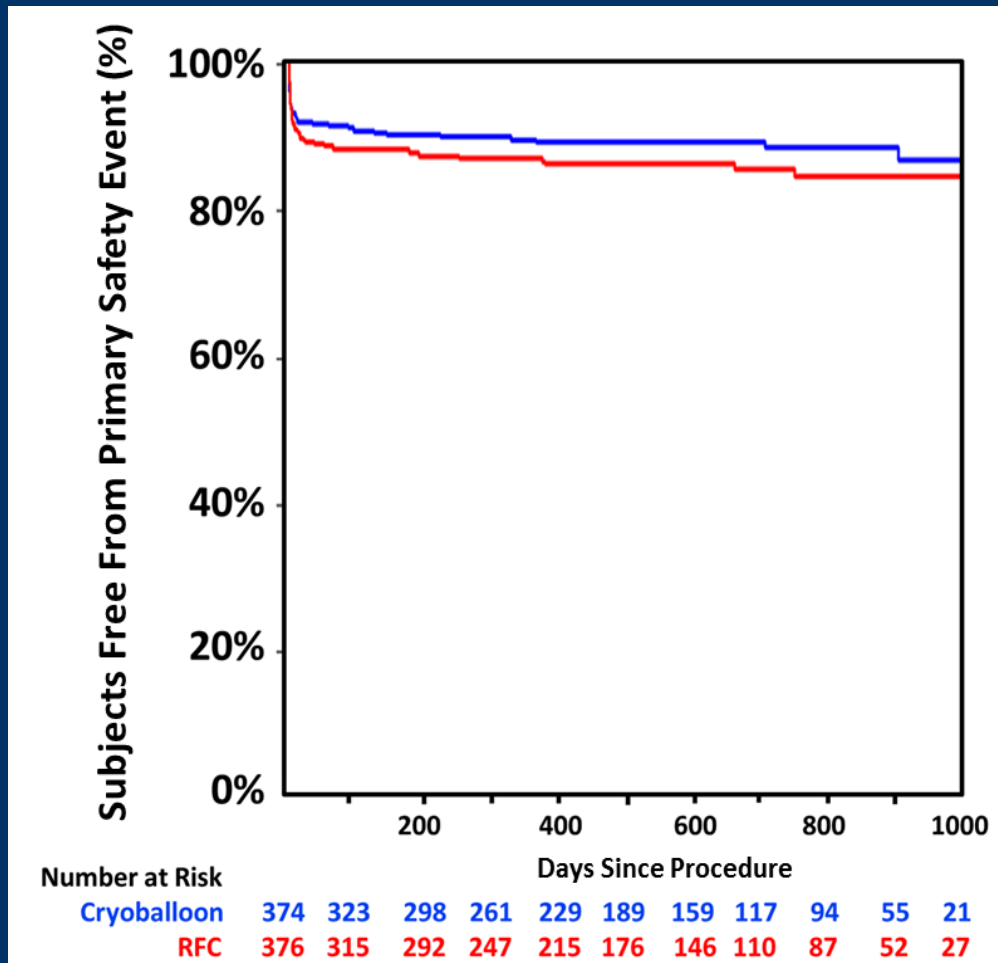
Primary Efficacy by Catheter Category



Log-rank test:
No significant heterogeneity
($p = 0.25$)

Number at Risk		Days Since Procedure										
		90	83	58	42	36	32	30	24	21	15	8
Arctic Front		90	83	58	42	36	32	30	24	21	15	8
Arctic Front Advance		279	251	183	151	128	99	76	45	35	19	4
THERMOCOOL/THERMOCOOL SF		284	260	187	151	121	104	84	54	42	23	10
THERMOCOOL SMARTTOUCH		93	90	55	40	28	15	9	4	2	1	

Primary Safety Endpoint Met



Modified ITT analysis

HR [95% CI] = 0.78 [0.52-1.18]; p = 0.24

Safety Event Type	RFC (n=376)	Cryoballoon (n=374)
All-cause death*	0	2
All-cause stroke/TIA	2	2
Arrhythmia-related SAE	13	8
Non-arrhythmia-related SAE	36	28
Total	51	40

* *Unrelated to treatment/device*

Key Treatment-Related Serious Adverse Events

Event (N, %)	RFC (n=376)	Cryoballoon (n=374)
Groin Site Complication*	16 (4.3%)	7 (1.9%)
Atrial Flutter/Atrial Tachycardia**	10 (2.7%)	3 (0.8%)
Phrenic Nerve Injury unresolved at discharge	0 (0%)	10 (2.7%)***
<i>Unresolved at 3 months</i>	0 (0%)	2 (0.5%)
<i>Unresolved at > 12 months</i>	0 (0%)	1 (0.3%)
Cardiac Tamponade/Pericardial Effusion	5 (1.3%)	1 (0.3%)
Stroke/TIA	2 (0.5%)	2 (0.5%)
Atrial Septal Defect	1 (0.3%)	0 (0%)
Esophageal Ulcer	0 (0%)	1 (0.3%)
Pericarditis	0 (0%)	1 (0.3%)
Atrioesophageal Fistula	0 (0%)	0 (0%)
Pulmonary Vein Stenosis	0 (0%)	0 (0%)

* Includes vascular pseudoaneurysm, AV fistula, device-related infection, hematoma, puncture site hemorrhage, groin pain

** Serious (e.g. hospitalization) and causally related to the therapeutic intervention (e.g. ablation-induced or drug-induced)

*** 8 resolved by 3 month visit, 1 resolved by 6 months visit, 1 unresolved after 12 month visit

Procedural Characteristics

Shorter, More Consistent* Procedure Times with the Cryoballoon

Time Measurement (minutes)	RFC (n=376)	Cryoballoon (n=374)	P-value**
Procedure Time***	140.9 ± 54.9	124.4 ± 39.0	<0.0001
LA Dwell Time***	108.6 ± 44.9	92.3 ± 31.4	<0.0001
Fluoroscopy Time	16.6 ± 17.8	21.7 ± 13.9	<0.0001

* Standard deviations were smaller in the cryoballoon group for all three procedure time measures, indicating more consistent times with less variation from the mean.

** t-test

*** Protocol required 30 min. waiting period after last application to assess PV isolation.

Secondary Analyses Results

Secondary Analysis Background

Secondary parameter analysis important in a comprehensive clinically meaningful evaluation

Published studies have reported:

- Nearly 40% hospitalization rates <1 year post-AF ablation^{1,2}
- AF-related readmission rates as high as 22%^{1,2}
- Approximately 10% of patients have a repeat ablation <1 year^{1,2,3}

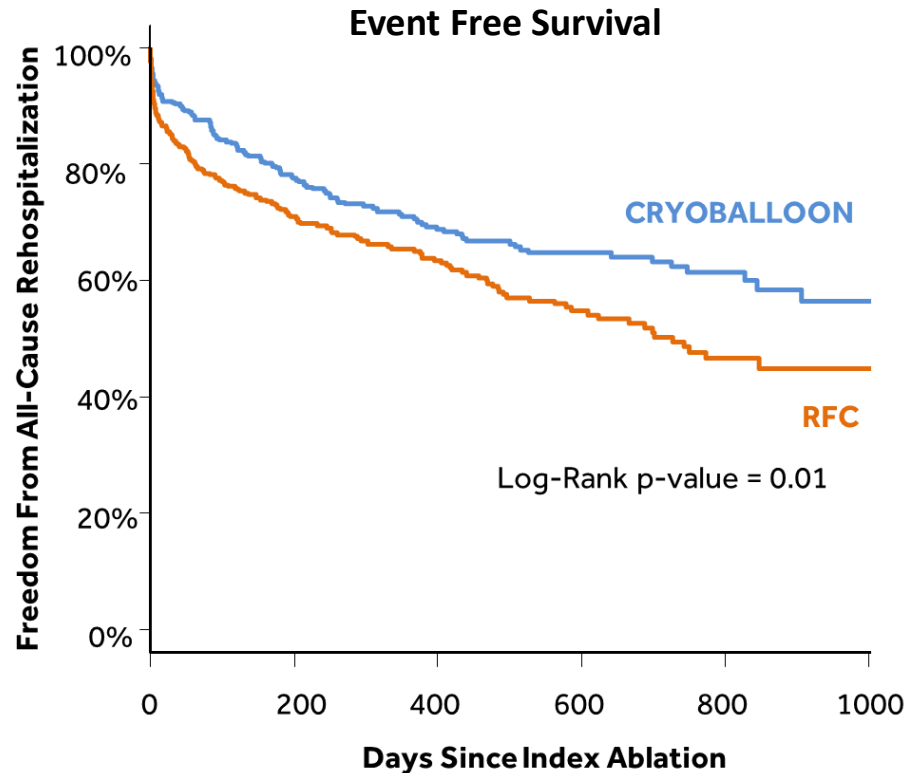
Secondary analyses included⁴:

- Cardiovascular hospitalization* (including AF hospitalization†)
- Repeat ablation*
- Quality-of-life*
- All-cause hospitalization
- Direct current cardioversion (DC Cardioversion)

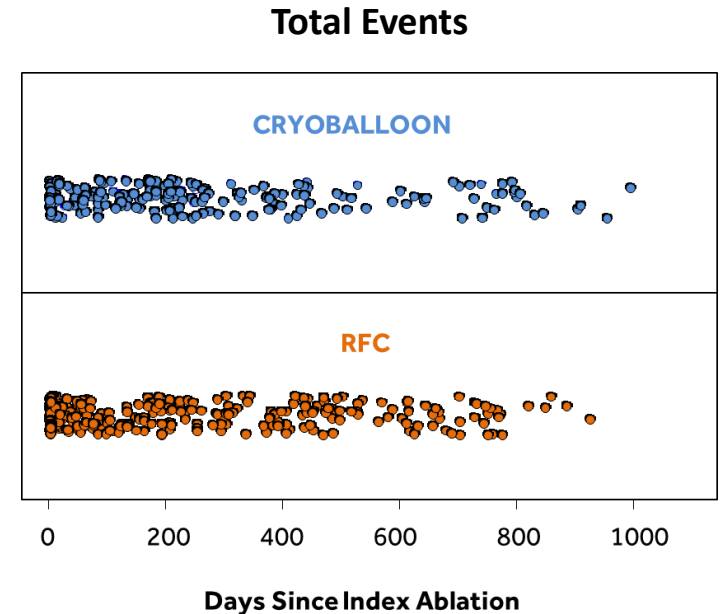
* Predefined secondary analyses

† Not predefined but included in analyses

Freedom From All-Cause Hospitalization



Number at Risk						
CRYOBALLOON	374	257	174	113	56	13
RFC	376	235	157	90	43	10

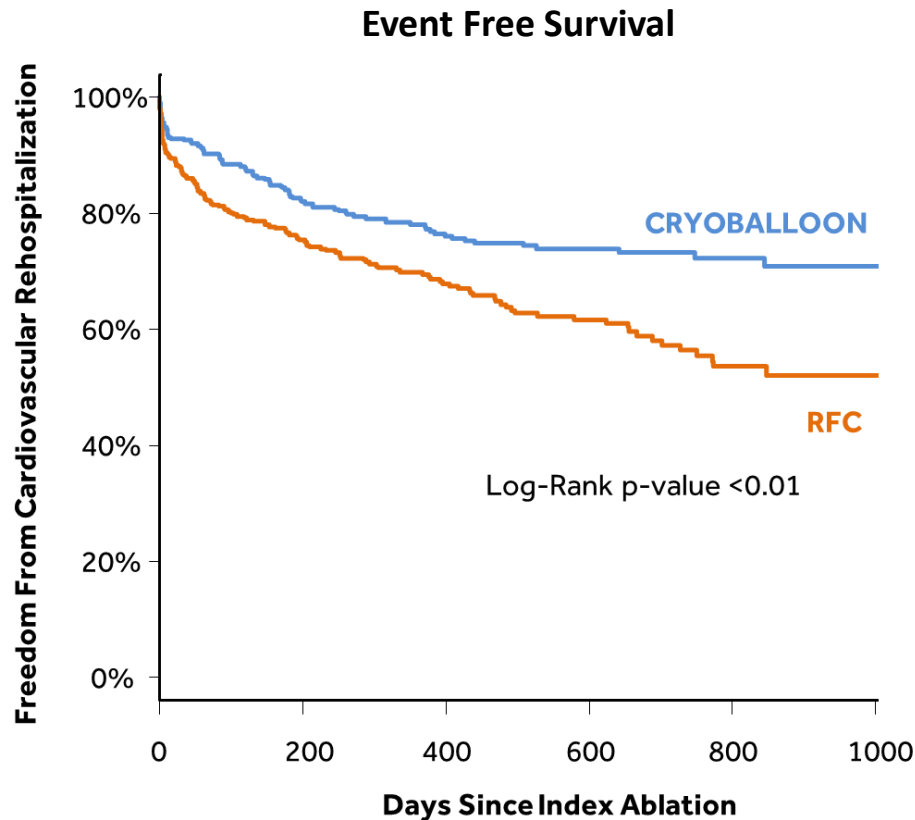


Modified ITT Analysis

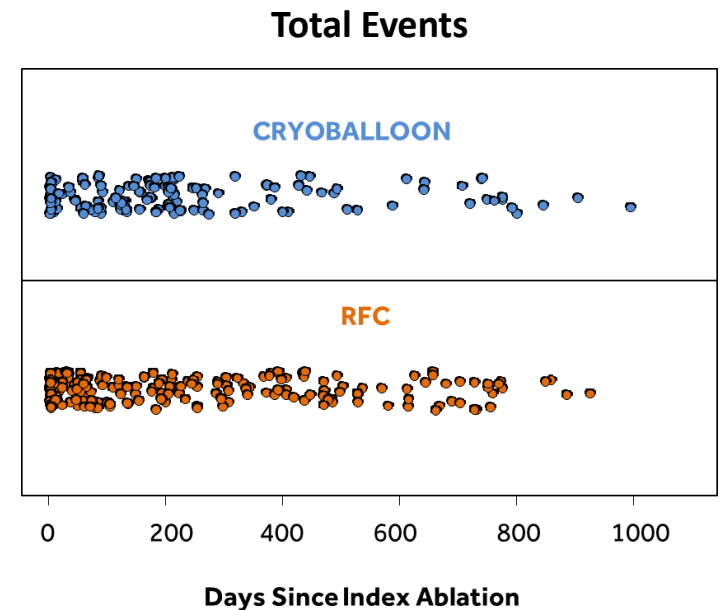
Cryo: 210 events in 122 subjects (122/374; **32.6%**)

RFC: 267 events in 156 subjects (156/376; **41.5%**)

Freedom From Cardiovascular Hospitalization



Number at Risk							
CRYOBALLOON	374	271	190	126	68	15	
RFC	376	250	167	102	52	14	



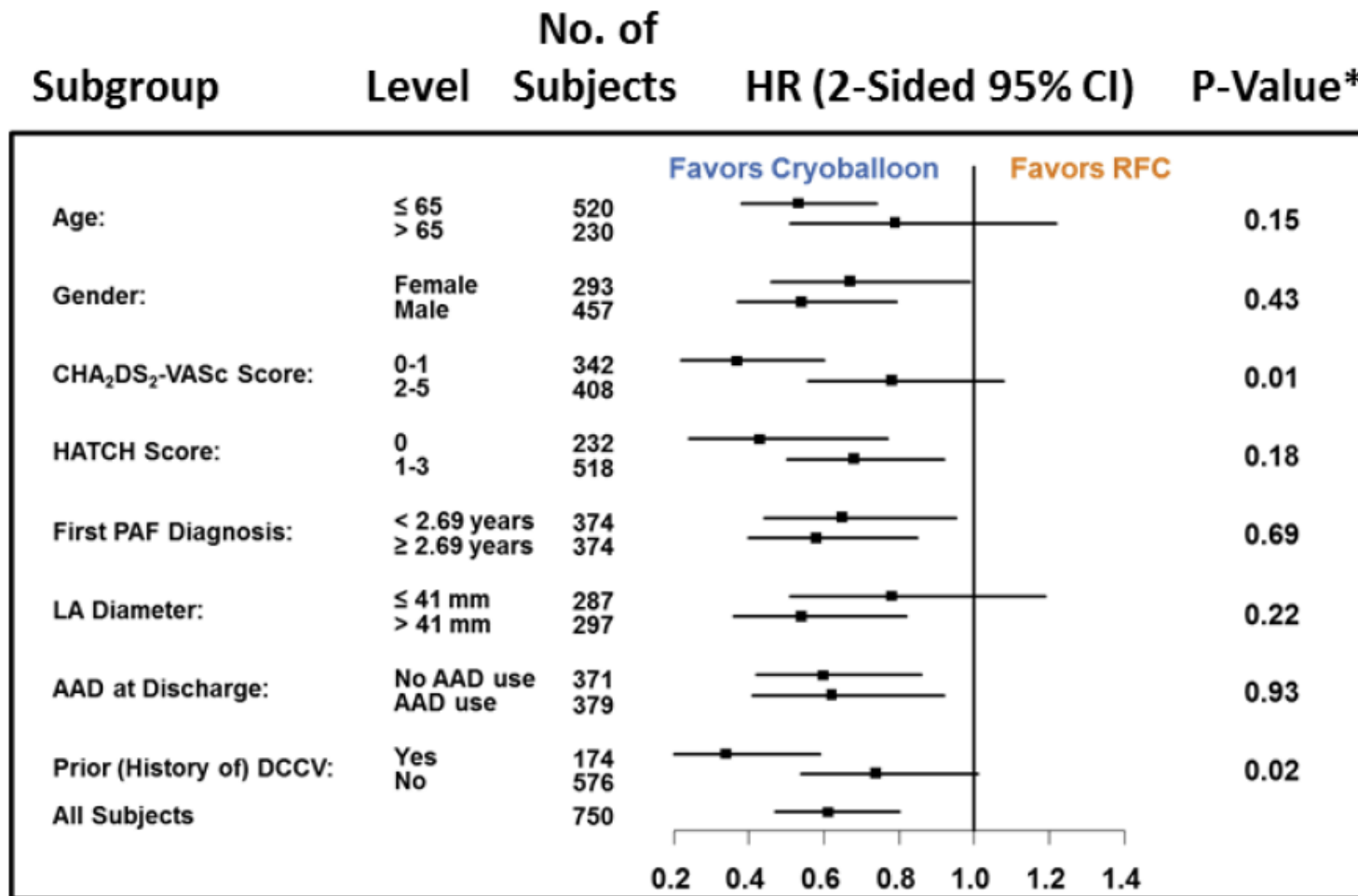
Modified ITT Analysis

Cryo: 139 events in 89 subjects
(89/374; **23.8%**)

RFC: 203 events in 135 subjects
(135/376; **35.9%**)

Freedom from Cardiovascular Hospitalization

Subgroup analysis of Baseline Characteristics

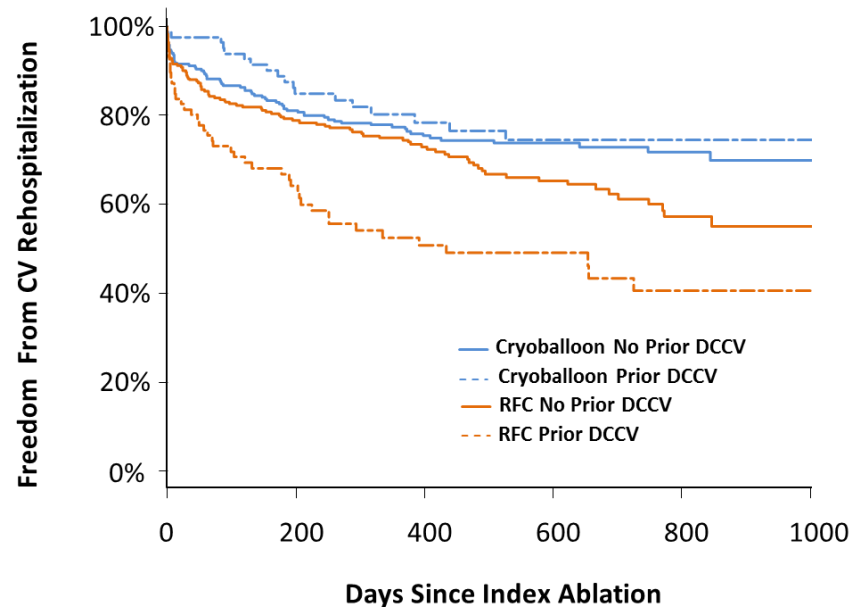


* P-Value from interaction term in Cox regression model

CI = confidence interval; HR = hazard ratio; PAF = paroxysmal atrial fibrillation; LA = left atrial;

AAD = antiarrhythmic drug; DCCV = direct current cardioversion

Freedom from Cardiovascular Hospitalization Subgroup Analysis of Subjects with Baseline DC Cardioversion



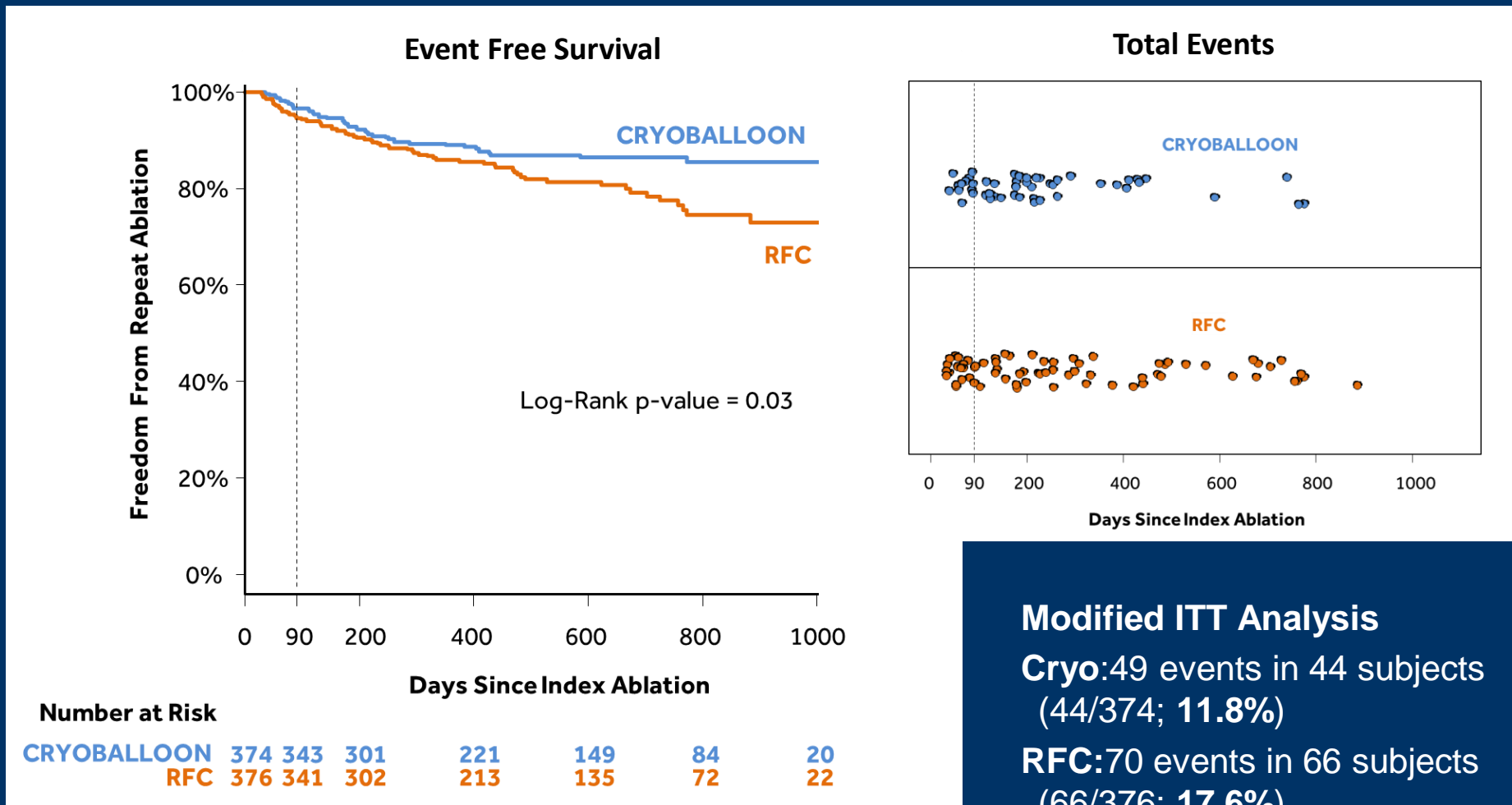
Number at Risk						
Cryoballoon No Prior DCCV	288	208	147	99	53	9
Cryoballoon Prior DCCV	86	63	43	27	15	6
RFC No Prior DCCV	288	204	136	80	40	10
RFC Prior DCCV	88	46	31	22	12	4

Cardiovascular Hospitalization

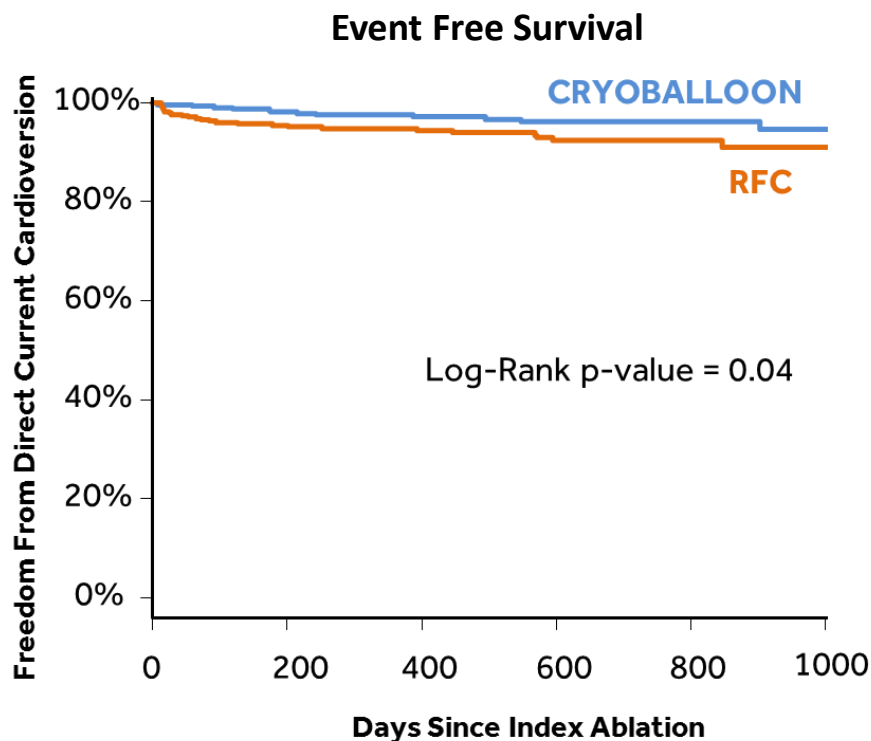
	Subjects with a CV Hospitalization (n, %)	P-Value*
Cryoballoon No Prior DCCV	71/288 (24.7%)	<0.01
RFC No Prior DCCV	92/288 (31.9%)	
Cryoballoon Prior DCCV	18/86 (20.9%)	=0.05
RFC Prior DCCV	43/88 (48.9%)	

* P-value from interaction term in Cox regression model

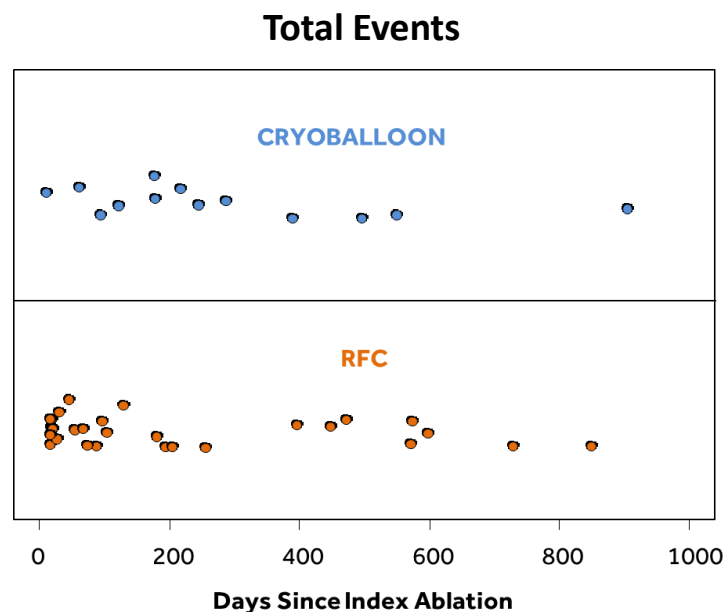
Freedom From Repeat Ablation



Freedom From DC Cardioversion



Number at Risk						
CRYOBALLOON	374	321	247	170	100	24
RFC	376	320	235	162	96	30

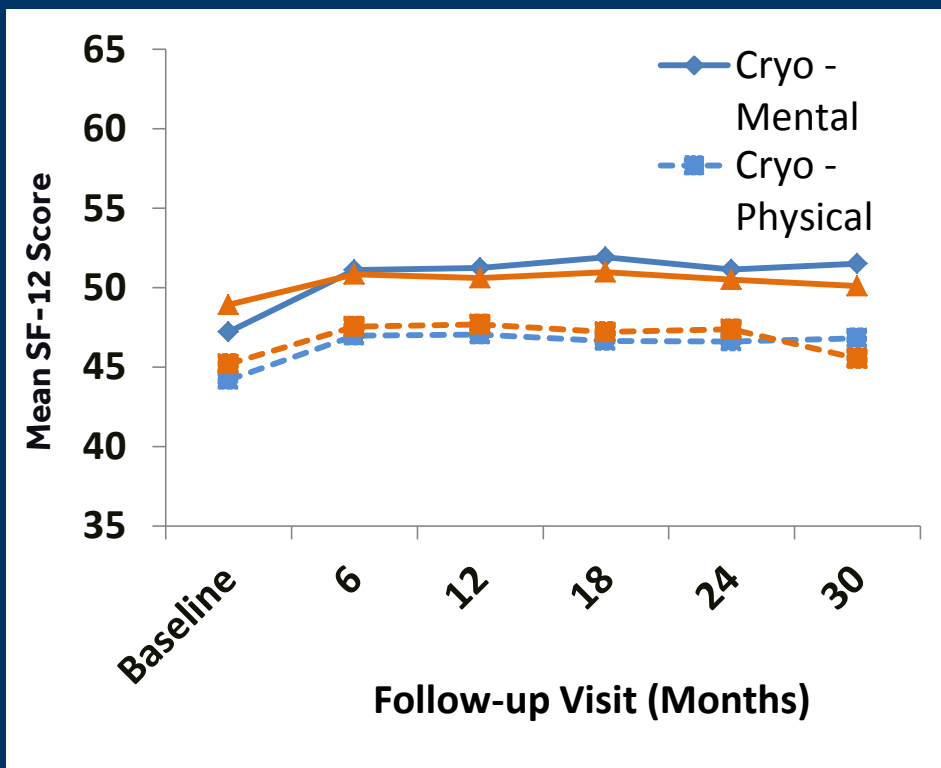


Modified ITT Analysis

Cryo: 13 events in 12 subjects
(12/374; 3.2%)

RFC: 28 events in 24 subjects
(24/376; 6.4%)

Subject Quality-of-Life



Summary of SF-12 Data at Baseline and 6 Months

		Baseline	6 Months	Δ	P-Value*
Cryoballoon N=258	Mental	47.1±10.3	51.1±8.9	4.0±9.8	<0.01
	Physical	43.7±9.1	47.0±9.1	3.2±8.2	<0.01
RFC N=267	Mental	48.9±9.8	50.8±8.8	1.9±9.9	<0.01
	Physical	44.5±9.5	47.6±8.6	3.1±8.6	<0.01

* t-test

Quality-of-life improved during follow-up in both groups and was maintained throughout 30 months

FIRE AND ICE Study Conclusions

- Primary Endpoints: PVI by cryoballoon ablation was found to be non-inferior to PVI by RFC ablation in terms of efficacy and safety, but had shorter and more consistent procedure times¹
- Subjects treated with cryoballoon compared to RFC had significantly fewer:²
 - Cardiovascular hospitalizations (including AF hospitalizations)
 - Repeat ablations
 - All-cause hospitalizations
 - Direct current cardioversions
- Both patient groups demonstrated improved quality-of-life scores after an AF ablation²
- These analyses have important implications on daily clinical practice

Arctic Front™ and Arctic Front Advance™ Cardiac CryoAblation Catheter Systems

Indications

- The Arctic Front Advance™ Cardiac CryoAblation Catheter catheter is indicated for the treatment of patients with atrial fibrillation (AF).

Contraindications

- Use of Arctic Front Advance™ Cryoballoon is contraindicated as follows:
- In the ventricle because of the danger of catheter entrapment in the chordae tendinae
- In patients with active systemic infections
- In conditions where the manipulation of the catheter within the heart would be unsafe (e.g., intracardiac mural thrombus)
- In patients with cryoglobulinemia
- In patients with one or more pulmonary vein stents

Brief Statement

- *Refer to the device technical manual for detailed information regarding the procedure, indications, contraindications, warnings, precautions, and potential complications/adverse events. For further information, please contact your Medtronic Sales Representative and/or consult Medtronic's website at www.medtronic.com.*

Backup

Committees

Steering Committee

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Dr. Riccardo Cappato
Milan, IT

Dr. David Wyn Davies
London, UK

Dr. Jan Tijssen – Statistician
Amsterdam, NL

Patient Enrollment by Center

Investigator	Center	Country	Enrolled	Treated
Prof. Dr. Karl-Heinz Kuck	Asklepios Klinik St. Georg, Hamburg	Germany	162	157
Dr. Julian Chun	Cardioangiologisches Centrum Bethanien CCB, Frankfurt	Germany	136	131
Dr. Arif Elvan	Isala Klinieken, Zwolle	The Netherlands	78	74
Prof. Dr. Thomas Arentz	University Heart Center Freiburg, Bad Krozingen	Germany	67	66
PD Dr. Michael Kühne	Universitätsspital, Basel	Switzerland	50	50
Dr. Laszlo Gellér	Semmelweis Egyetem, Budapest	Hungary	47	47
Dr. Matthias Busch	Universitätsmedizin, Greifswald	Germany	35	33
Dr. Lluís Mont	Hospital Clinic de Barcelona, Barcelona	Spain	32	32
Dr. Alberto Barrera	Hospital Clínico Universitario "Virgen de la Victoria", Malaga	Spain	30	30
PD Dr. Thomas Deneke	Herz- und Gefäß-Klinik, Bad Neustadt	Germany	27	26
Dr. Jean-Paul Albenque	Clinique Pasteur, Toulouse	France	26	26
Prof. Dr. Volker Kühlkamp	Herz-Zentrum Bodensee, Konstanz	Germany	22	22
Prof. Dr. Claudio Tondo	Centro Cardiologico Monzino University of Milan, Milan	Italy	18	18
Dr. Ricardo Ruiz-Granell	Hospital Clinico Universitario, Valencia	Spain	17	16
Doz. Petr Neuzil	NA Homolce Hospital, Prague	Czech Republic	12	12
Dr. Nicasio Pérez-Castellano	Hospital Clinico San Carlos, Madrid	Spain	10	10
TOTAL			769	750