Cryoballoon or RF Ablation for Paroxysmal AF
The FIRE AND ICE Trial

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Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation The FIRE AND ICE Trial

(ClinicalTrials.gov NCT01490814)

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AT THE INTERSECTION OF SCIENCE & CHANGE

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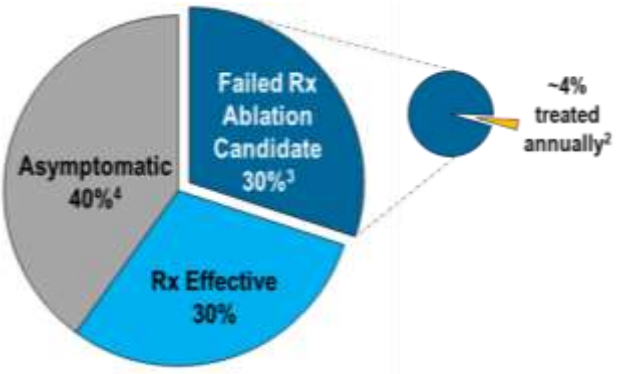
Background

- **Atrial fibrillation (AF) is the most common arrhythmia with a prevalence >33 million[1]**
- **Catheter ablation is a Class I Level A recommendation for treatment of symptomatic patients with paroxysmal AF (PAF) refractory or intolerant to ≥1 Class I or III antiarrhythmic drugs (AAD)[5]**
- **Pulmonary vein isolation (PVI) is the cornerstone of AF ablation strategy[6]**



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Background

- **FIRE AND ICE is the largest randomized trial to evaluate the efficacy and safety of cryoballoon ablation vs. radiofrequency current (RFC) ablation in patients with PAF**
- **Two AF ablation strategies were widely marketed in 2012**
  - **RFC ablation with THERMOCOOL® (Biosense Webster, Inc.) catheters utilizing CARTO® 3D electroanatomical mapping**
  - **Cryoballoon ablation with Arctic Front™ (Medtronic, Inc.) catheters utilizing fluoroscopic guidance**

2007	2012	2015	2016
HRS/EHRA/ECAS: Lack of data for *"single shot"* devices	HRS/EHRA/ECAS: *"…RF is by far the dominant energy source…"*	FIRE AND ICE completed enrollment January 27th	FIRE AND ICE locked database freeze January 29th
	FIRE AND ICE enrolled first subject January 19th	FIRE AND ICE accrued 249 primary endpoints September 17th	

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Objectives/Hypothesis

- Compare the efficacy and safety of Pulmonary-Vein Isolation 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 a hazard ratio (HR) of 1.43
- Primary Safety Endpoint: Time to first all-cause death, all-cause stroke/TIA or treatment-related SAEs (e.g. phrenic nerve injury, atrioesophageal fistula etc.)

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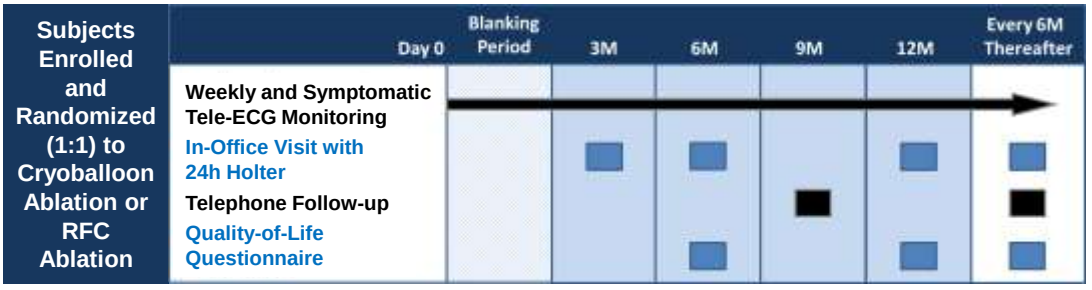
Methods

- Key Inclusion Criteria
  - Symptomatic PAF
  - Prior AAD failure
  - 18 – 75 years of age
- Key Exclusion Criteria
  - Previous LA ablation or surgery
  - PCI, MI within 3 months of enrollment
  - Stroke/TIA within 6 months of enrollment
  - LVEF <35%
  - LA diameter > 55 mm



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Methods

- Investigators must have documented experience
  - ≥ 50 cases with either ablation technique; 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, but no additional lines or CFAE ablation)
- Must confirm PVI 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 at day of procedure

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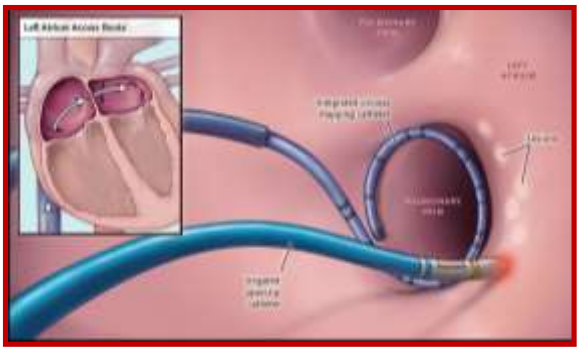
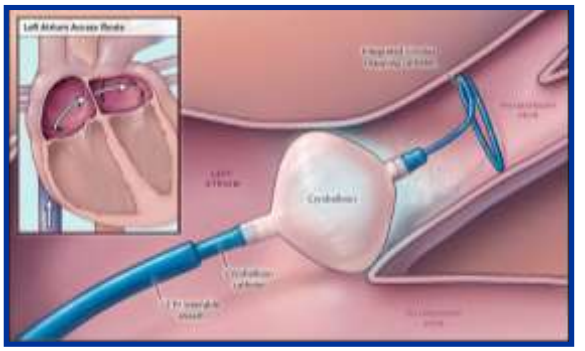
Methods

- RFC Ablation ("FIRE")
  - Power was not to exceed
    - 40 W at A/I aspect
    - 30 W 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



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Committees

- **Steering Committee**
  - **Prof. Dr. Karl-Heinz Kuck – PI**
    Hamburg, DE
  - **Dr. Jean-Paul Albenque**
    Toulouse, FR
  - **Prof. Dr. Josep Brugada**
    Barcelona, ES
  - **Prof. Dr. Claudio Tondo**
    Milan, IT
  - **Prof. Dr. Stuart Pocock**
    London, UK
  - **PD Dr. Kurt Bestehorn**
    Munich, DE
  - **Dr. Alexander Fürnkranz**
    Frankfurt, DE
- **Independent Event Review Committee**
  - **Prof. Dr. Thorsten Lewalter – Chairman**
    Munich, DE
  - **Dr. Malte Kuniss**
    Bad Nauheim, DE
  - **Prof. Dr. Lars Lickfett**
    Mönchengladbach, DE
- **Independent Data and Safety Monitoring Board**
  - **Prof. Dr. Hein J.J. Wellens – Chairman**
    Maastricht, NL
  - **Dr. Riccardo Cappato**
    Milan, IT
  - **Dr. David Wyn Davies**
    London, UK
  - **Dr. Jan Tijssen – Statistician**
    Amsterdam, NL

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RESULTS

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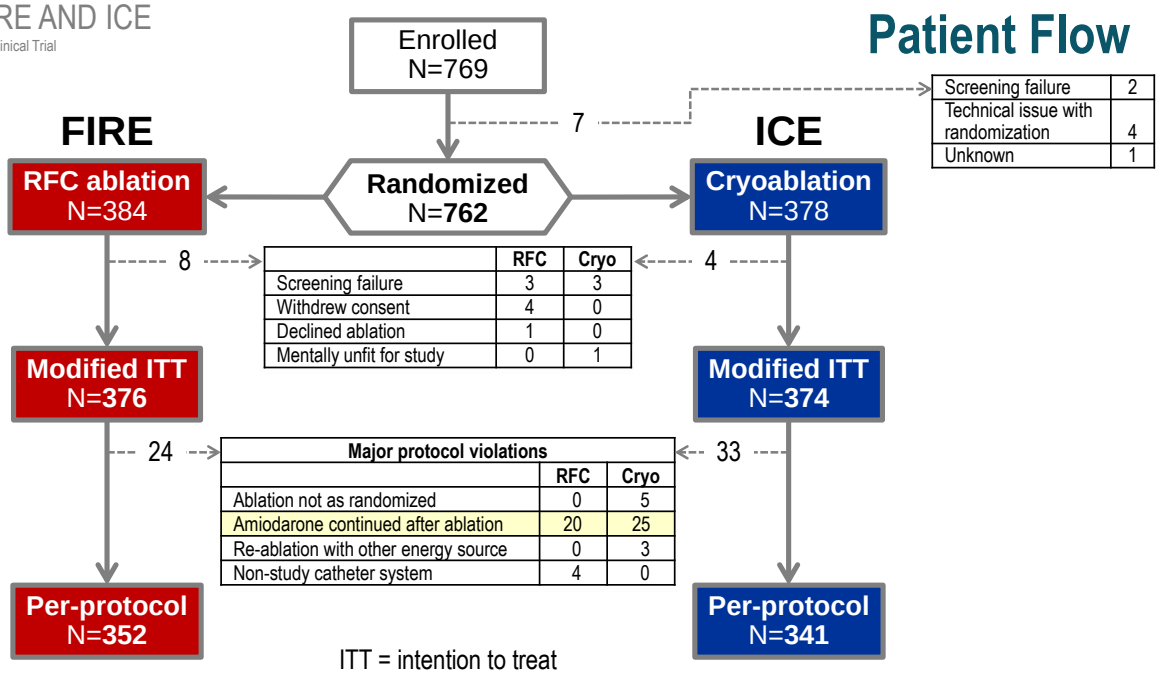
Patient Flow



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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. Lluis 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

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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_2DS_2-VASc Score, n (%)			0.19**
0	58 (15.5)	67 (17.8)	
1	108 (28.9)	109 (29.0)	
2	95 (25.4)	97 (25.8)	
3	60 (16.0)	62 (16.5)	
4	40 (10.7)	33 (8.8)	
5	10 (2.7)	7 (1.9)	
6	3 (0.8)	1 (0.3)	
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	24%	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

* *t-test for continuous variables, Fisher's exact test for dichotomous variables*
** *Cochran-Mantel-Haenszel statistics*

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%

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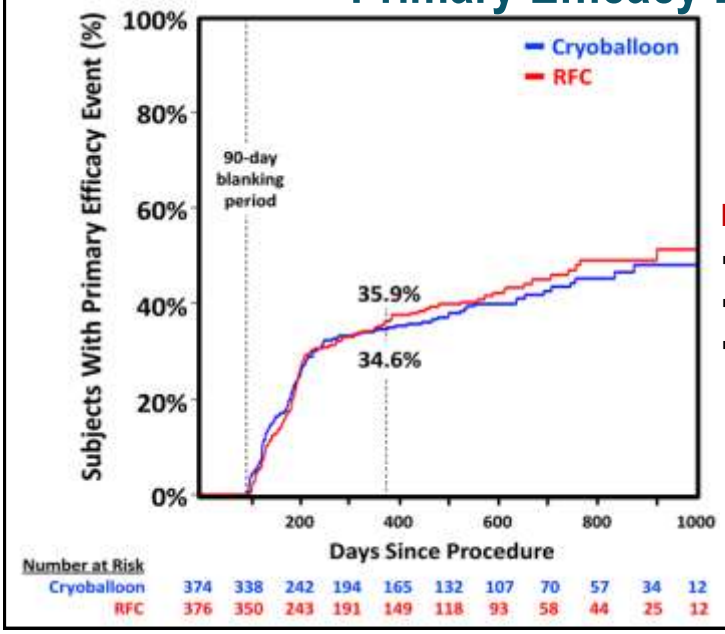
Primary Efficacy End Point



Modified ITT analysis

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

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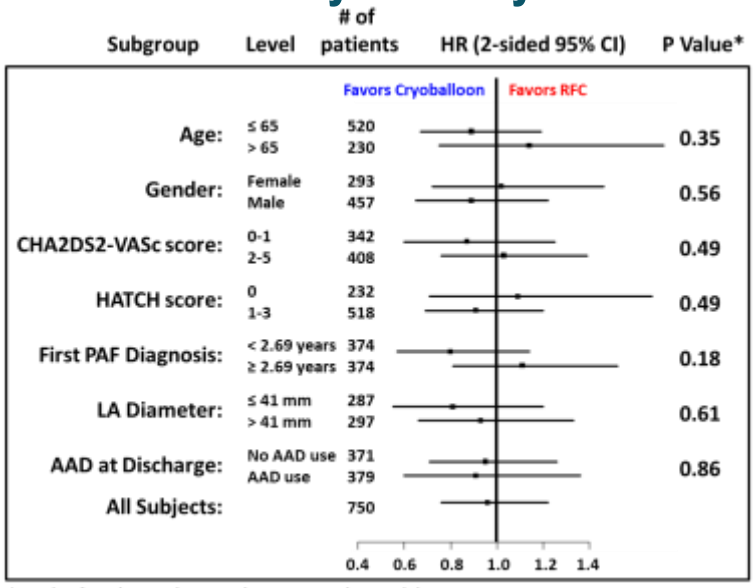
Primary Efficacy End Point: Subgroups



* P value from interaction term in Cox regression model
CI = confidence interval; HR = hazard ratio; PAF = paroxysmal atrial fibrillation

Modified ITT analysis

- Subgroups predefined in study protocol

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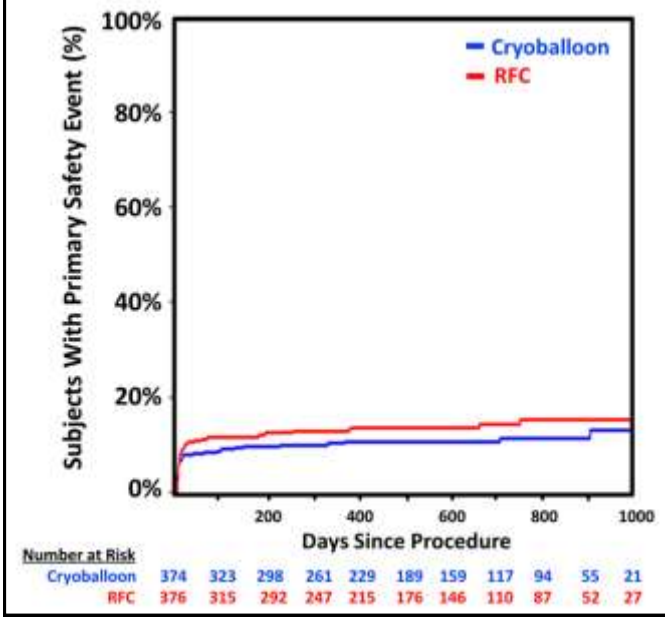
Primary Safety End Point



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*

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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**	**10 (2.7%)*****
Unresolved at 3 months	0	2 (0.5%)
Unresolved at > 12 months	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**
Esophageal Ulcer	**0**	**1 (0.3%)**
Pericarditis	**0**	**1 (0.3%)**
Atrioesophageal Fistula	**0**	**0**
Pulmonary Vein Stenosis	**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*

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Procedural Characteristics

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**

* *Calculations based on mITT*
** *t-test*
*** *Protocol required 30-min waiting period after last application to assess PVI*

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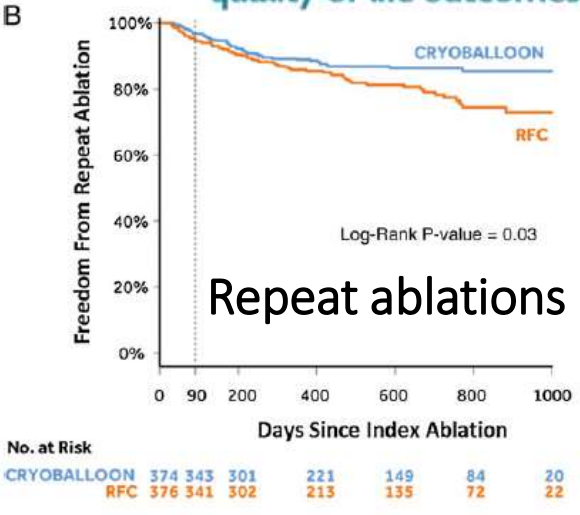
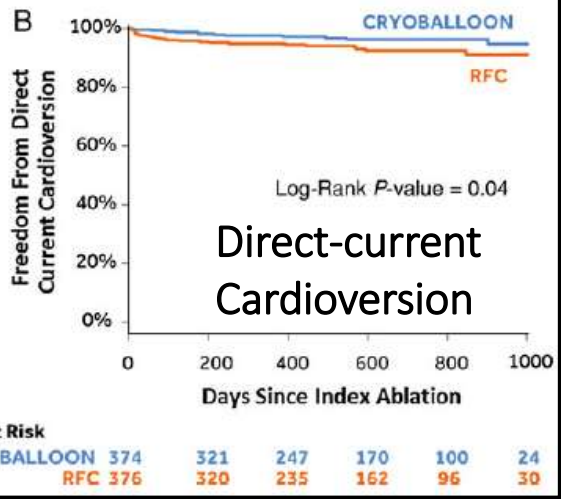
Cryoballoon or radiofrequency ablation for symptomatic paroxysmal atrial fibrillation: reintervention, rehospitalization, and quality-of-life outcomes in the FIRE AND ICE trial



Repeat ablations



Direct-current Cardioversion

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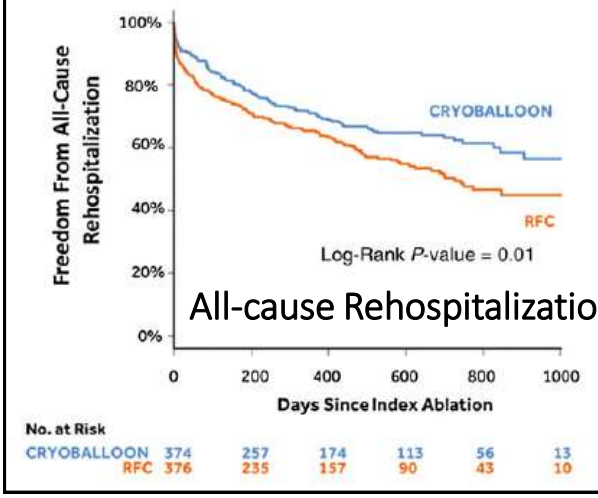
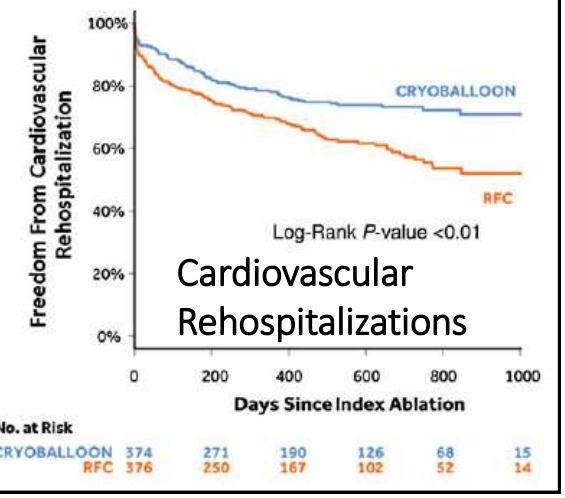


All-cause Rehospitalizations



Cardiovascular Rehospitalizations

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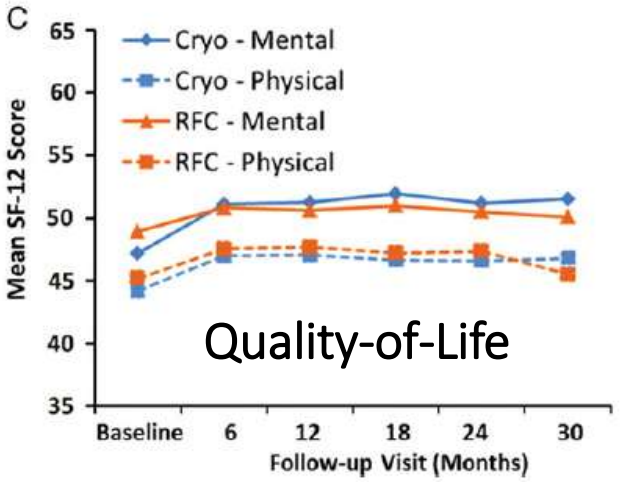

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Conclusions

- FIRE AND ICE was a large, rigorous, randomized trial conducted by experienced AF ablation practitioners
  - A favorable safety profile was observed in both groups
- Significant procedural differences between groups
  - RFC ablation required less fluoroscopy time
  - Cryoablation procedure and LA dwell times were shorter
- The FIRE AND ICE trial found that pulmonary-vein isolation by cryoballoon ablation to treat patients with paroxysmal atrial fibrillation was non-inferior to pulmonary-vein isolation by radiofrequency ablation in terms of efficacy and safety
- Cryoballoon ablation conveys Less repeat ablations, Less DCC, Less rehospitalizations and Similar QOL

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