



Crioablazione: fast-track della fibrillazione atriale parossistica

Raimondo Calvanese



Pulmonary Vein Isolation is the Cornerstone of AF Ablation



> 90%

Of AF triggers found near PVs¹

2020 ESC AF Guidelines

PVI is the best documented target for catheter ablation and the cornerstone of all AF ablation procedures²

- "The cornerstone of AF catheter ablation is the complete isolation of pulmonary veins by linear lesions around their antrum..."²
- "AF catheter ablation is a well-established treatment for the prevention of AF recurrences. When performed by appropriately trained operators, AF catheter ablation is a safe and superior alternative to AADs for maintenance of sinus rhythm and symptom improvement"²

2017 HRS/EHRA Consensus Statement

"Electrical isolation of the PVs is recommended during all AF ablation procedures (Class I, LoE A)"³

Growing Body of Published Literature

5 RCTs demonstrated no benefit in ablation beyond PVI for AF (n > 1,100) $^{4-8}$

1. Haïssaguerre M, et al. N Engl J Med 1998; 339:659-666 2. Hindricks, G., et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). European Heart Journal, 1–126. 2020 3. Calkins H, et al. Heart Rhythm. 2017 Oct;14(10):e275-e444. 4. Verma A, et al. N Engl J Med. 2015;372:1812–1822 5. Wong KC, et al. Circ Arrhythm Electrophysiol. 2015; 8:1316–1324 6. Verma A, et al. J Cardiovasc Electrophysiol. 2011 May;22(5):541-547 7. Dixit S, et al. Circ Arrhythm Electrophysiol. 2012;5:287-294 8. Vogler J, et al. J Am Coll Cardiol. 2015 Dec 22;66(24):2743-2752

2020 ESC Guidelines for the management of atrial fibrillation



Hindricks, G., et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). European Heart Journal, 1–126. 2020.

Perché anticipare un'ablazione di fibrillazione atriale?

AF Disease Progression

Paroxysmal AF develops into persistent AF with an overall rate of 5.5% per year¹



1. Kato T, et al. Circ J (2004) 68: 568 2. Kirchhof et al. 2016 Guidelines for the management of AF developed in collaboration with EACTS. Eur Heart J. 2016;37:2893-2962 3. Nattel et al. Early management of atrial fibrillation to prevent cardiovascular complications. Eur Heart J. 2014; 35(22):1448-56 4. Schotten et al. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. Physiol Rev. 2011; 91:265-325 5. Zhao et al. Observation of the efficacy of radiofrequency catheter ablation on patients with different forms of atrial fibrillation. Euro Rev Med Pharmacol Sci. 2016; 20:4141-47 6. Quan et al. Predictors of late atrial fibrillation recurrence after cryoballoon-based pulmonary vein isolation: a meta-analysis. Kardiologia Polska. 2017; 75(4):376-85

Consequences of Atrial Fibrillation Progression Increased mortality risk

Rocket-AF Trial

- 14,062 AF patients
 - 18% paroxysmal
 - 82% persistent
- Paroxysmal AF patients had significantly lower rates of:
 - All-cause mortality (adjusted HR: 0.79)
 - Stroke (adjusted HR: 0.78)
 - Composite of stroke, systemic embolism, and death (adjusted HR: 0.82)
 - P < 0.05 for all outcomes



Morbidity and Mortality

AF progression is associated with increased morbidity and mortality^{1,2}

- 2.5x yearly cardiovascular event rate (permanent vs. non-permanent AF)³
- 6.5x prevalence of stroke (persistent vs. paroxysmal AF)⁴
- 2.5x prevalence of heart failure (persistent vs. paroxysmal AF)⁴
- ~ 1.5x increased hospitalizations for cardiovascular problems and ≥2x for electrical cardioversions or stroke/transient ischemic attack (progression vs. no progression)⁵
- Decreased health-related quality of life (EuroQoL-5D) due to worsening AF symptoms and adverse events (progression vs. no progression)⁶

and adverse events (progression vs. no progression)*

1. Kato T, et al. Circ J (2004) 68: 568 2. Steinberg et al. Higher risk of death and stroke in patients with persistent vs. paroxysmal atrial fibrillation: results from the ROCKET-AF Trial. Europace. 2016; 18: 648-57 3. De With RR et al. Atrial fibrillation progression and outcome in patients with young-onset atrial fibrillation. Europace. 2018; [Epub ahead of print] 4. Almeida ED et al. Clinical differences between subtypes of atrial fibrillation and flutter: cross-sectional registry of 407 patients. Arq Bras Cardiol. 2015; 105(1):3-10 5. de Vos CB et al. Progression from paroxysmal to persistent atrial fibrillation: clinical correlates and prognosis. JACC. 2010; 55(8):725-731 6. Dudink et al. The influence of progression of atrial fibrillation on quality of life: a report from the Euro Heart Survey. Europace. 2018; 20:929-934

Preventing Progression Of AF: How To Treat?

Ablation reduces the percentage of AF progression vs. medical therapy alone

- Systematic review in general population (primarily medical therapy only) vs. catheter ablation studies
- Weighted progression from paroxysmal to persistent or permanent AF by followup duration
- The percentage of AF progression increases over time (i.e., with longer follow up duration) in general population studies (n = 21), but remains flat in AFablation studies (n = 8)



Proietti *et al*. A systematic review on the progression of paroxysmal to persistent atrial fibrillation: shedding new light on the effects of catheter ablation. *JACC: Clinical Electrophysiology*. 2015; 1(3):105-115.

Earlier Treatment can improve Clinical Outcomes

RF ablation for Persistent AF

- Two-year outcomes were assessed in 1241 consecutive patients undergoing first-time ablation of Persistent AF
- B-type natriuretic peptide levels, Creactive protein levels, and left atrial size were associated with arrhythmia recurrence
- Shorter diagnosis-to-ablation times were associated with improved ablation outcomes
 - In direct association with markers of atrial remodeling



Figure 2. Kaplan–Meier curves presenting success of ablation of persistent atrial fibrillation as a function of the quartiles of the time interval between the very first diagnosis and the ablation procedure.

EARLY-AF Study Design



Objective:	To determine if first-line cryoballoon ablation was superior to first-line antiarrhythmic drug (AAD) therapy as assessed by an insertable cardiac monitor (ICM).
Study Size:	303 patients from 18 sites in Canada.
rimary Endpoint:	Time to first recurrence of any (symptomatic or asymptomatic) atrial tachyarrhythmia (AF/AFL/ or AT) ≥30 sec between days 91 and 365 after treatment initiation
Secondary Endpoints:	 Time to first recurrence of symptomatic atrial tachyarrhythmia 91 and 365 days after treatment initiation Total arrhythmia burden (% of time in AF, as detected by continuous monitoring) Repeat ablation procedures Quality of life (QoL) Emergency visit or hospitalization >24 hour in a health-care facility Serious adverse events

EARLY-AF Patient Flow



*Enrollment Permitted If:

- 1. AAD Treatment Naïve Never treated with an AAD
- 2. Current AAD use Treatment <6 months below therapeutic threshold
- **3. Previous AAD use** Treatment initiated,
 discontinued and washed
 out >6 months prior to
 enrollment
- 4. Temporary AAD use Treatment at therapeutic dose for <4 weeks; no adverse drug effects or inefficacy

No crossovers prior to primary endpoint failure

**Potential arrhythmia events detected by the device were stored for adjudication by an independent, blinded clinical endpoint committee

EARLY-AF Baseline Characteristics

Characteristic	AAD (n=149)	Ablation (n=154)
Age, years	59.5±10.6	57.7±12.3
Male sex	102 (68.5%)	112 (72.7%)
Obesity (BMI >30)	53 (35.6%)	56 (36.6%)
AF duration (yrs. from diagnosis)	1 (0, 4)	1 (0, 3)
Paroxysmal AF	140 (94.0%)	147 (95.5%)
Symptomatic AF episodes/mo.	3 (1, 10)	3 (1, 10)
Previous cardioversion	63 (42.3%)	56 (36.4%)
CHA ₂ DS ₂ -VASc	1.9±1.0	1.9±1.1
Hypertension	55 (36.9)	57 (37.0%)
Ischemic heart disease	7 (4.7%)	12 (7.8%)
Sleep apnea	32 (21.5%)	32 (20.8%)
Previous stroke or TIA	5 (3.4%)	4 (2.6%)
Stable Heart Failure	14 (9.4%)	14 (9.1%)
LA volume, ml/m²	35.4±12.5	35.6±15.2
LVEF, %	59.8±7.6	59.6±7.0
Beta-blocker	92 (61.7%)	85 (55.2%)
Previous class I or III AAD drug	44 (29.5%)	40 (26.0%)

- The population was relatively young and healthy
- 1-year median duration from first AF diagnosis
- On average, 3 symptomatic AF episodes per month
- 39% had prior cardioversion

EARLY-AF Primary Outcome

Freedom From Any Atrial Tachyarrhythmia on Continuous Monitoring

FREEDOM FROM PRIMARY ENDPOINT FAILURE AT 12 MONTHS WAS 57.1% IN THE ABLATION GROUP VS. 32.2% IN THE AAD GROUP



EARLY-AF Secondary Outcomes Freedom From Symptomatic Arrhythmia Recurrence

FREEDOM FROM SYMPTOMATIC ARRHYTHMIA RECURRENCE WAS HIGHER IN THE ABLATION GROUP (89.0%) VS. AAD GROUP (73.8%) AT 12 MONTHS



EARLY-AF Secondary Outcomes AF Burden

PATIENTS IN THE ABLATION GROUP SPENT LESS TIME IN AF THAN PATIENTS IN THE DRUG GROUP



EARLY-AF Secondary Outcomes Arrhythmias

FREEDOM FROM ARRHYTHMIA RECURRENCE WAS HIGHER WITH ABLATION VS. DRUG THERAPY

Outcome	AAD n=149	Ablation n=154	Treatment Effect HR (95% CI)	P-Value
Freedom from symptomatic atrial tachyarrhythmia (with blanking period)	110 (73.8%)	137 (89.0%)	0.39 (0.22, 0.68)	<0.001
Freedom from any AF (with blanking period)	58 (38.9%)	94 (61.0%)	0.51 (0.37, 0.70)	<0.001
Freedom from symptomatic AF (with blanking period)	111 (74.5%)	138 (89.6%)	0.38 (0.21, 0.67)	<0.001
Freedom from any atrial tachyarrhythmia after multiple ablation procedures	48 (32.2%)	102 (66.2%)	0.38 (0.27, 0.53)	<0.001
Freedom from symptomatic atrial tachyarrhythmia after multiple ablation procedures	110 (73.8%)	143 (92.9%)	0.26 (0.13, 0.51)	<0.001
Days in AF	16.8±46.9	3.4±16.5		<0.001

EARLY-AF Secondary Outcomes Quality of Life and Symptom Status

ABLATION WAS ASSOCIATED WITH LARGER IMPROVEMENTS IN QOL AND A HIGHER RATE OF SYMPTOM RESOLUTION

Outcome	AAD n=149	Ablation n=154	Treatment Effect	Important difference
Change in AFEQT (baseline to 6 months)	17.9±1.6	24.4±1.6	10.5±2.2*	5 points
Change in AFEQT (baseline to 12 months)	22.9±2.0	26.9±1.9	8.0±2.2*	
Change in EQ-5D (baseline to 6 months)	0.07±0.02	0.08±0.02	0.03±0.03*	0.03-0.05 points
Change in EQ-5D (baseline to 12 months)	0.06±0.02	0.12±0.02	0.07±0.03*	
Change in EQ-VAS (baseline to 6 months)	4.97±1.19	6.10±1.17	2.05±1.68*	7-8 points
Change in EQ-VAS (baseline to 12 months)	5.71±1.46	7.73±1.44	2.94±1.69*	
Asymptomatic at 6 months	90 (62.9%)	129 (84.8%)	1.34 (1.17, 1.55)**	
Asymptomatic at 12 months	109 (76.2%)	131 (89.1%)	1.17 (1.05 <i>,</i> 1.30)**	

EARLY-AF Adverse Events

Characteristic	AAD (n=149)	Ablation (n=154)
Serious adverse event	6 (4.0%)	5 (3.3%)
Any safety endpoint event	24 patients, 27 events	14 patients, 15 events
CARDIAC		
Pericardial effusion requiring drainage	1	0
Heart failure exacerbation	1	0
Syncope	2	1
Wide complex tachycardia	2	0
Bradycardia or AV block requiring pacemaker	2	2
Acute coronary syndrome	2	0
NEUROLOGICAL		
Stroke	0	0
ΤΙΑ	1	0
VASCULAR		
Hematoma not requiring intervention	0	1
DVT	0	1

EARLY-AF Conclusions

First-line ablation was associated with significant reduction in arrhythmia outcomes:

- Time to first recurrence of any AF/AFL/AT
- Time to first recurrence of any AF
- Time to first recurrence of symptomatic AF/AFL/AT
- Time to first recurrence of symptomatic AF
- Total AF burden
- Days with AF

First-line ablation was associated with meaningful improvements in QoL and symptoms

Adverse events were similar between contemporary cryoballoon ablation and AAD therapy

Cryo-FIRST Study Design

Objective:	Evaluate the effectiveness of pulmonary vein isolation (PVI) performed with the Arctic Front™ Advance Cardiac CryoAblation Catheter System as first-line therapy in comparison with antiarrhythmic drugs (AAD) in patients with paroxysmal atrial fibrillation (PAF)
Study Size:	220 patients enrolled by 18 sites
Primary Endpoint:	Freedom from any atrial arrhythmia (AA) longer than 30 seconds after blanking
Quality of Life:	AF-specific quality of life was evaluated using the Atrial Fibrillation Effect on QualiTy-of- Life (AFEQT) questionnaire
AA monitoring:	7 day Holter at 1,3,6,9,12 month follow up classified by an independent core lab

Key Inclusion Criteria

Symptomatic paroxysmal atrial fibrillation (< 7 days)

- ≥ 2 symptomatic episodes (past 6 month)
- ≥ 1 documented AF episode (past 1 year)

Structural normal heart

(LVEF \geq 50%; IV septum \leq 12mm; LAD < 46mm) Normal ECG

(QRS width \leq 120ms; QTc < 440ms; PQ \leq 210ms)

Age 18-75 years

Key Exclusion Criteria

- Persistent AF or atrial flutter
- Class I or III AAD treatment
- Left atrial ablation
- Permanent pacemaker
- Cardiac surgery
- TIA or stroke
- Intra-cardiac thrombus formation
- NYHA class II, III or IV

Kuniss et al. Cryoballoon ablation vs. antiarrhythmic drugs: first-line therapy for patients with paroxysmal atrial fibrillation. Europace (2021) 00, 1–9.

Cryo-FIRST Primary Endpoint (ITT analysis)



Cryoballoon catheter ablation was associated with a **>50% risk reduction** in atrial arrhythmia recurrence compared to AAD therapy over 12 months in the Cryo-FIRST study

Kuniss et al. Cryoballoon ablation vs. antiarrhythmic drugs: first-line therapy for patients with paroxysmal atrial fibrillation. Europace (2021) 00, 1-9.

Cryo-FIRST Time to First Serious AE



There was no difference in time-to-first SAE

In addition, there was

- No death
- No phrenic nerve injuries after the hospital discharge
- No atrio-esophageal fistula
- No pericardial tamponade
- No stroke

Cryo-FIRST Quality of Life

Atrial Fibrillation Effect on QualiTy-of-life - ITT							
Follow Up visit	Drug Therapy	Cryo Ablation	Adjusted Mean Diff. (95% CI)	Adjusted Mean Di	fference (95% CI)	p-value	
Baseline	107	105	0.9 (-3.2 - 4.9)		-	0.670	
1M FU	98	90	1.5 (-2.7 - 5.8)	_	•	0.477	
3M FU	96	89	10.0 (5.7 - 14.3)			<.001	
6M FU	94	90	6.7 (2.4 - 11.0)			0.002	
9M FU	93	87	9.0 (4.6 - 13.4)			<.001	
12M FU	92	89	9.9 (5.5 - 14.2)			<.001	
				← Drug Therapy Better	Cryo-Ablation Better →		
				-15 -10 -5 (0 5 10 15		

- A statistically significant and clinically meaningful improvement for the AFEQT summary score was observed after Cryoballoon catheter ablation compared to AAD therapy at 3, 6, 9 and 12 months
- At 12 months, more patients in the cryoablation group were without symptoms (EHRA score 1) compared to the patients in the AAD group (86.5% vs. 70.4%, P=0.017)

Chierchia, GB., et al. Quality of Life Measured in First-Line Therapy During the Cryo-FIRST Study: A Comparison Between Cryoballoon Catheter Ablation Versus Antiarrhythmic Drug Therapy. Poster presented at the 2020 ESC Congress – The Digital Experience.

Cryo-FIRST Conclusion





Cryoablation was superior to AAD therapy, significantly reducing AA recurrence in previously drug treatment naïve (first-line) patients with symptomatic PAF¹





A similar safety profile was observed in both arms when examining SAEs during the study¹

Fellow Up visit	Drug Therapy	Cryo Abiation	Adjusted Mean Diff. (95% CI)	Adjusted Mean D	fference (95% CI)	p-value
Baseline	107	105	0.9 (-3.2 - 4.9)	1	-	0.670
1M FU	98	90	1.5 (-2.7 - 5.8)	2	<u>.</u>	0.477
3M FU	96	89	10.0 (5.7 + 14.3)		-	< 001
6M FU	94	90	6.7 (2.4 - 11.0)			0.002
9M FU	93	87	9.0 (4.5 - 13.4)			<.001
12M FU	92	89	99(55-142)			< 001
				- Orug Therapy Setter	Cryo-Ablahon Better	t.:
				-15 -10 -5 (5 10 15	

AF-Specific quality of life was significantly higher in the catheter ablation group at 3, 6, 9 and 12 month follow-up²

1. Kuniss et al. Catheter Cryoablation Versus Antiarrhythmic Drug as First-Line Therapy of Paroxysmal Atrial Fibrillation (Cryo-FIRST). Presented at the German Cardiac Society conference DGK 2020. 2. Chierchia, GB., et al. Quality of Life Measured in First-Line Therapy During the Cryo-FIRST Study: A Comparison Between Cryoballoon Catheter Ablation Versus Antiarrhythmic Drug Therapy. Poster presented at the 2020 ESC Congress – The Digital Experience.

STOP AF First Study Design

DESIGN: FDA regulated, prospective, randomised multicenter study (24 US sites)

PATIENT POPULATION: Drug naïve (not on AAD for \geq 7 days) with symptomatic PAF, aged 18-80

RANDOMIZATION: randomised 1:1 to pulmonary vein isolation (PVI) with the Arctic Front[™] Advance Cryoballoon (Medtronic) or AAD therapy (Class I or III)

Arrhythmia Monitoring:

Monitoring	Baseline	1 M	3 M	6 M	12 M
12-Lead ECG	Х	Х	Х	Х	Х
24 Hr Continuous Ambulatory ECG				Х	Х
Patient-Activated Ambulatory ECG (TTM; Weekly and when Symptomatic)		_			



STOP AF First Primary Efficacy Endpoint



Freedom from primary efficacy failure at 12 months:

- Cryoballoon: 75% (95% CI: 65-82%)
- AAD: 45% (95% CI: 35-55%)

STOP AF First Primary Safety Endpoint

Estimated 12-month Rate Of Primary Safety Events: 1.9% (95% CI: 0.5 – 7.5%)



Primary Safety Events:

- Development of a significant pericardial effusion within 30 days
- Myocardial infarction within 7 days

Additionally, an AAD arm patient had a major vascular complication following a cryoballoon ablation.

First-line Cryoablation Trials

	Cryo-FIRST	STOP AF First	EARLY-AF	
# Sites (# Enrollments)	20 in Europe, Argentina and Australia (220 pts)	24 in the US (225 pts)	18 in Canada (303 pts)	
Monitoring Used	7-day Holter	24hr Holter, patient-activated TTMs (weekly and when symptomatic)	LINQ ICM+ 24 hr. Holters	
Ablation Strategy	PVI completion / focal trigger allowed w/ Freezor MAX; re- ablation allowed during blanking	Only PVI in LA, no re-ablation procedures allowed	PVI only, no re-ablation procedures allowed	
Primary Endpoint	Freedom from AF/AT/AFL>30 sec	Treatment success (no acute procedural failure, AF/AT/AFL >30 sec, (re)ablation, cross-over)	Freedom from AF/AT/AFL>30 sec	
		Safety (ablation arm only; pre- specified performance goal)		
Safety Evaluation	Time to first SAE	Pre-specified procedure and/or system-related serious adverse events – <i>compared to performance</i> goal	Major complications	
Quality of Life	AFEQT and SF-36	AFEQT and EQ-5D (changes evaluated only in the ablation arm)	AFEQT and EQ-5D	

First-line cryoablation evidence Consistent Efficacy results

Differences in the freedom from primary efficacy endpoint failure due in part to

- Primary endpoint definitions
- Modality of cardiac monitoring during follow-up



ALL 3 TRIALS DEMONSTRATE THAT AS A FIRST-LINE TREATMENT, CRYOBALLOON IS SUPERIOR TO AAD FOR PREVENTION OF ATRIAL ARRHYTHMIA RECURRENCE

First-line cryoablation evidence Consistent safety results

Cryo-FIRST and EARLY-AF evaluated all serious adverse events, whereas primary safety events in STOP AF First only included a select list of pre-specified procedure and system-related serious adverse events



Conclusioni



La Fibrillazione è una malattia cronica progressiva

Una strategia di iniziale di crioablazione

- Efficace nel ridurre le recidive aritmiche senza incrementare gli eventi avversi rispetto alla terapia antiaritmica
- Migliora la qualità della vita
- Bassi tempi procedurali



Conclusioni

Quello che le LG non ci dicono:

Fattore TEMPO

Un intervento precoce nella storia naturale della fibrillazione atriale può limitare la progressione della malattia e migliorare gli outcome



Scacco al Rischio **Evitabile** Strategie per Ridurre il Rischio di Eventi

Cardiovascolari







Earlier ablation decreases the risk of repeat ablation FIRE AND ICE

- 750 subjects with symptomatic paroxysmal AF:
 - Refractory to class I or III antiarrhythmic drugs
 - Cryoballoon or RF catheter ablation
- Each additional year between AF diagnosis and ablation procedure was associated with a 3% increased risk of repeat ablation (HR = 1.03; P = 0.039)
- Higher freedom of AF predictor for patients who did not undergo cardioversions



Earlier Treatment Reduces Risk Of Recurrence Meta-analysis On Earlier Treatment



Patients treated with an ablation less than 1 year after diagnosis have a 27% lower risk of AF recurrence after ablation

41 Chew DS, Black-Maier E, Loring Z, et al. Diagnosis-to-Ablation Time and Recurrence of Atrial Fibrillation Following Catheter Ablation: A Systematic Review and Meta-analysis of Observational Studies Circ Arrhythm Electrophysiol. 2020 Apr;13(4):e008128 doi:10.1161/CIRCEP.119.008128

Early Rhythm Control Therapy EAST-AFNET4

- Study design: Prospective, randomised, Multicenter trial
- Aim: investigating whether an early, comprehensive, rhythm control therapy can prevent adverse cardiovascular outcomes in patients with atrial fibrillation (AF) compared to usual care (rate control).
- Patient population: Patients with an increased risk of stroke (CHA₂DS₂-VASc score of ≥2) and recednt-onset AF (≤ 1 year prior to enrolment)
- 2.810 patients were enrolled (2.789 randomised) from 140 centers in 11 European countries
- **Randomization**: Usual care vs. Early standardized rhythm control
- Primary Outcomes:
 - A composite of cardiovascular death, stroke and hospitalization due to worsening of heart failure or due to acute coronary syndrome
 - Nights spent in hospital per year



Cumulative Incidence of first primary outcome

The EAST trial results show that early treatment of AF with a structured follow-up:

- improves patient outcome with regards to CV death, stroke and hospitalization, and AF recurrence
- was **comparable in safety** when compared to usual care

Chew DS, Black-Maier E, Loring Z, et al. Diagnosis-to-Ablation Time and Recurrence of Atrial Fibrillation Following Catheter Ablation: A Systematic Review and Meta-analysis of Observational Studies Circ Arrhythm Electrophysiol. 2020 Apr;13(4):e008128 doi:10.1161/CIRCEP.119.008128

EARLY-AF Antiarrhythmic Drug Treatment Group

- Most patients were treated with flecainide or sotalol
- 31% of patients tried at least two drugs

Drug Used	First N (%)	Second N (%)	Third N (%)	Any Time N (%)	Median Dose Mg/day
Flecainide	114 (76.5%)	10 (6.7%)	0	124 (83.2%)	200 (125, 250)
Propafenone	7 (4.7%)	9 (6.0%)	2 (1.3%)	18 (12.1%)	600 (450, 600)
Sotalol	23 (15.4%)	17 (11.4%)	2 (1.3%)	42 (28.2%)	160 (160, 240)
Dronedarone	5 (3.4%)	7 (4.7%)	0	12 (8.1%)	800 (800, 800)
Amiodarone	0	3 (2.0%)	4 (2.7%)	7 (4.7%)	200 (200, 200)
Total	149 (100%)	46 (30.9%)	8 (5.4%)		

AF Disease Progression

Baseline echocardiographic variables, age, cardiomyopathy, and heart rate were independently associated with progression to chronic AF¹

Canadian AF Registry; CARAF N = 757 PAF pts; FU: 8 yrs.



After the initial diagnosis of paroxysmal AF, there is a slow but steady progression to chronic AF²

EuroHeart Survey, 2003-04

- N = 5333 AF pts; FU: 1 yrs.
- PAF 18 % \rightarrow persist/perm AF
- Pers. AF 30% \rightarrow perm AF
 - Rhythm control attempted in only 1/3 of pts progressing to persist AF



Progressive atrial Remodeling

- Continuous AF induces cardiac remodeling e.g., irreversible fibrosis³
- AF Patients with more atrial fibrosis are more likely to experience less favorable outcomes⁴
- Longer diagnosis to ablation time for PersAF is associated with markers of atrial remodeling⁵



1. Kerr CR, Am Heart J. 2005 2. Nieuwlaat, EurHeart J 2008; 29,1181–89 3. Shinagawa K, et al. Circulation (2002) 105: 2672 4. Marrouche et al. JAMA. 2014;311(5):498-506. doi:10.1001/jama.2014 5. Hussein et al. Circ Arrhythm Electrophysiol. 2016 Jan;9(1):e003669

2020 ESC Guidelines for the management of atrial fibrillation

The Class IIa, level B recommendation for first-line paroxysmal AF ablation is supported by the MANTRA-PAF, RAAFT-1, and RAAFT-2 radiofrequency ablation trials:

First-line therapy		
AF catheter ablation for PVI should/may be considered as first-line rhythm control therapy to improve symptoms in selected patients		
with symptomatic:		
 Paroxysmal AF episodes,^{240-242,614,615} or 	lla	В
 Persistent AF without major risk factors for AF recurrence. 	IIb	С
as an alternative to AAD class I or III, considering patient choice, benefit, and risk.		
AF catheter ablation:		
 Is recommended to reverse LV dysfunction in AF patients when tachycardia-induced cardiomyopathy is highly probable, inde- pendent of their symptom status.^{666,675,676} 	1	В
 Should be considered in selected AF patients with HF with reduced LVEF to improve survival and reduce HF hospitalization.^{612,659,662-666,668-671,817-826} 	lla	в
AF catheter ablation for PVI should be considered as a strategy to avoid pacemaker implantation in patients with AF-related bradycar- dia or symptomatic pre-automaticity pause after AF conversion considering the clinical situation. ^{816–818}	lla	с

First-line ablation meta-analysis

1212 patients from 6 randomised clinical trials were included in the meta-analysis: Cryo-FIRST, EARLY-AF, STOP AF First, RAAFT-1, RAAFT-2, MANTRA-PAF.

- Catheter ablation was associated with a 38% reduction in recurrence of atrial arrhythmias and 68% reduction in hospitalisations compared with AAD therapy
- There was no significant difference in the composite of major adverse events between the two groups.



STOP AF First Patient Baseline Characteristics

Participants were relatively healthy with few comorbidities

	Cryoballoon Catheter Ablation (n=104)	AAD (n=99)
Age, years	60.4 ± 11.2	61.6 ± 11.2
Gender, male	61%	58%
Time from PAF onset, years	1.3 ± 2.5	1.3 ± 2.3
Left atrial diameter, mm	38.7 ± 5.7	38.2 ± 5.4
Hypertension	56%	58%
Diabetes	14%	17%
Congestive heart failure	1%	3%
Stroke	0%	3%
Valve dysfunction	8%	9%
CHA ₂ DS ₂ -VASc Score		
0	19%	16%
1	27%	28%
2	32%	19%
3	12%	22%
> 3	11%	14%
Electrical cardioversion in the previous 12 months	18%	15%
Pharmacological cardioversion in the previous 12 months	8%	14%

STOP AF First Conclusions

Freedom from primary efficacy failure at 12 months was 75% for the Cryoballoon arm and 45% for the AAD arm (p<0.0001)

Two primary safety events (1.9%) were observed in the catheter ablation arm

RAAFT-1 TRIAL

- 70 patients with symptomatic AF were randomised to either AAD therapy (N=37) or RF ablation (N=33)
- Primary efficacy outcome: Recurrence of

 (a)symptomatic AF (>15 sec) occurred in 63% of
 patients in the AAD group vs. 13% of patients in the
 ablation group (P<0.001)

Secondary efficacy outcomes:

- Hospitalization rate during 1Y FU occurred in 54% in AAD arm vs 9% in ablation arm (P<0.001)
- QoL (SF36) improvement at 6M FU significantly better in ablation arm then in AAD arm.
- Safety: There were no thromboembolic events in either group. Asymptomatic mild or moderate PV stenosis was documented in 2 (6%) patients in the ablation arm.



RAAFT-2 TRIAL

- 127 treatment-naïve PAF patients randomised to either AAD therapy or RF ablation
- Primary efficacy outcome: Recurrence of any atrial tachyarrhythmia (>30 sec.) occurred in 72.1% of patients in the AAD group vs. 54.5% of patients in the ablation group
- Secondary efficacy outcomes: Recurrence of symptomatic AF occurred in 57.4% of patients in the AAD group vs. 40.9% of patients in the ablation group
- Safety: The ablation group had a 9% rate of serious adverse events, the most frequent of which was pericardial effusion with tamponade experienced by 4 patients (6%)



MANTRA-PAF TRIAL

- Prospective multicentre study with 294 patients randomised to either a point-by-point RF ablation or AAD therapy arm
- **Primary endpoint:** the cumulative and per-visit burden of atrial fibrillation (2-year follow-up)
 - No significant differences in cumulative AF burden
 - (ablation: 13%; AAD: 19%; P= 0.10)
 - AF burden was significantly lower in the ablation group after 24 months (9% vs. 18%; P = 0.007)
- Secondary outcome: significantly improved freedom from AF in the ablation group (85% vs. 71%, P = 0.004)
 - Non-significant reduced time to first recurrence of AF in the ablation group HR 0.79 (0.57-1.09; P = 0.16)
- Safety: One death in the ablation group was due to a procedure-related stroke; there were three cases of cardiac tamponade in the ablation group.



AF-specific quality of life with first-line cryoablation

Cryo-FIRST

The adjusted mean AFEQT summary score was significantly higher in the cryoballoon vs. AAD arm at 3, 6, 9 and 12 months, and the mean difference was clinically meaningful (>5 points)

Follow Up visit	Drug Therapy	Cryo Ablation	Adjusted Mean Diff. (95% CI)	Adjusted Mean Di	fference (95% CI)	p-value
Baseline	107	105	0.9 (-3.2 - 4.9)	_	-	0.670
1M FU	98	90	1.5 (-2.7 - 5.8)	_	-	0.477
3M FU	96	89	10.0 (5.7 - 14.3)			<.001
6M FU	94	90	6.7 (2.4 - 11.0)			0.002
9M FU	93	87	9.0 (4.6 - 13.4)		_ 	<.001
12M FU	92	89	9.9 (5.5 - 14.2)			<.001
				← Drug Therapy Better	Cryo-Ablation Better	,
				-15 -10 -5 (0 5 10 15	

Cryo-FIRST AND EARLY-AF DEMONSTRATE THAT CRYOBALLOON ABLATION IS SUPERIOR TO AAD THERAPY FOR IMPROVING AF-SPECIFIC HEALTH-RELATED QUALITY OF LIFE

EARLY-AF

First-line ablation was associated with meaningful improvements in AFEQT at 6 and 12 months compared to AAD therapy

Change in AFEQT	Antiarrhythmic Drug n=149	Ablation n=154	Treatment Effect HR (95% CI)	Important difference
6 months	17.9±1.6	24.4±1.6	10.5±2.2*	5 points
12 months	22.9±2.0	26.9±1.9	8.0±2.2*	
*LSMD±SE				

Freedom from symptoms with first-line cryoablation

Cryo-FIRST At 12 months, 86.5% of	Outcome	Antiarrhythmic Drug n=111		Ablation n=107	
patients in the ablation arm vs. 70.4% of patients in the AAD		Baseline	12 Months	Baseline	12 Months
arm were without AF-related symptoms (EHRA score 1;	EHRA I (No symptoms)	0.0%	86.5%	0.0%	70.4%
1 -0.017).					
EARLY-AF At 12 months, 89% of patients in the ablation arm and 76% of	Outcome		Antiarrhythmic Drug n=149	Ablation n=154	Treatment Effect HR (95% CI)
patients in the AAD arm were without AE-related symptoms	Asymptomatic at 6 mo	onths	90 (62.9%)	129 (84.8%)	1.34 (1.17, 1.55)
(CCS-SAF Symptom Score 0)	Asymptomatic at 1 mo	onths	109 (76.2%)	131 (89.1%)	1.17 (1.05, 1.30)

Cryo-FIRST AND EARLY-AF DEMONSTRATE THAT CRYOBALLOON ABLATION IS SUPERIOR TO AAD THERAPY REDUCING AF-RELATED SYMPTOMS

Medtronic

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first-line Ablation

ESC Guidelines for the Diagnosis and Management of AF

AF Progression

Importance of Early Ablation Treatment

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Consistent Results Across various centers

Arctic Front Advance[™] Cryoballoon single-center published studies demonstrating single procedure freedom from AF, AT, and AFL after one year



(Freedom from AF Only or AF/AT/AFL) varied between studies

Di Giovanni, et al. J Cardiovasc Electrophysiol. 2014; 25(8):834-839; Fürnkranz, et al. J Cardiovasc Electrophysiol. 2014;25(8):840-844; Aryana, et al. J Interv Card Electrophysiol. 2014;41(2):177-186; Aytemir, et al. Europace. 2015;17(3):379-387; Greiss, et al. PACE. 2015 Jul;38(7):815-824; Metzner, et al. Circ Arrhythm Electrophysiol. 2014;7(2):288-292; Chierchia, et al. Europace. 2014; Chierchia, et al. J Cardiovasc Electrophysiol. 2015;16(5):639-644; Kumar, et al. J Interv Card Electrophysiol. 2014;41(1):91-97; Jourda, et al. Europace. 2015;17(2):225-231; Ciconte, et al. Heart Rhythm. 2015;12(4):673-680; Tebbenjohanns, et al. Europace. 2015; Wissner, et al. Europace. 2015;17(8):1236-1240

Cryoballoon Ablation

More consistent outcomes and procedure times

Among centers with varying annual ablation volume

	Cryoballoon ablation	Radiofrequency ablation	P-value
Procedure time (min)	120 ± 36	136 ± 57	p < 0.036
Fluoroscopy time (min)	23 ± 9	21 ± 13	p = 0.073

Major complications with significant differences:

Pericardial effusion	0.3%	1.7%	P = 0.036
PNI	1.8%	0.0%	P = 0.004



Compared to radiofrequency, outcomes were less operator dependent with cryoballoon

- AF ablation procedures caseload: <100 AF ablations/year < 100 AF ablations/year = 100-150 AF ablations/year = 200 AF ablations/year
 - = 500 AF ablations/year

*Cryoballoon ablation procedures were performed with first generation Arctic Front™ catheter and Flexcath™ steerable sheath. †Radiofrequency Group, WACA was performed using either a 3.5 or a 4 mm tip irrigated catheter guided by 3D mapping and navigation. The contact sensing catheters were used on 100/467 (21.4%) patients. Providencia R, et al. Results from a multicentre comparison of cryoballoon vs. radiofrequency ablation for paroxysmal atrial fibrillation: is cryoablation more reproducible? Europace. 2017 Jan;19(1):48-57

FIRE AND ICE Trial: Primary Endpoints¹

Trial design and methods:

The FIRE AND ICE AF Ablation Clinical Trial is the largest prospective, 1:1 randomised, non-inferiority study (762 patients from 16 sites in eight countries) that compared the efficacy and safety of PVI using cryoballoon vs. radiofrequency (RFC) ablation with the CARTO[®] 3D mapping system in patients with paroxysmal atrial fibrillation (PAF)

Primary Efficacy Endpoint:

Time to first documented recurrence of AF > 30s/AT/AFL, prescription of AAD, or repeat ablation

Primary Safety Endpoint:

Time to first all-cause death, all-cause stroke/ TIA, or treatment-related serious AEs



Primary Efficacy Endpoint Results:

Cryoballoon met the noninferiority endpoint and did so with shorter and more consistent procedure times compared to radiofrequency.

Primary Safety Endpoint Results:

The primary safety endpoint was achieved. There was no significant difference between the two methods with regard to overall safety.

Favorable patient outcomes

Clinically relevant patient experiences

FIRE AND ICE Trial: secondary analysis—significant improvements favoring Cryoballoon In a pre-defined secondary analysis, relative to radiofrequency, cryo demonstrated¹:

European Heart Journal

The authors stated, "The extent of reduction in reinterventions and rehospitalizations is not only statistically significant but also clinically relevant. Our presented data are the main events that define the patients' perception regarding the procedural success of an AF ablation procedure."

34%

fewer cardiovascular hospitalizations

 \checkmark

Cyro: 139 events in 89 subjects (89/374;23.8%) RFC: 203 events 135 subjects (135/376; 35.9%)

32%

fewer repeat ablations

 \checkmark

Cyro: 49 events in 44 subjects (44/374; 11.8%) **RFC:** 70 events 66 subjects (66/376; 17.6%)

1. Kuck KH, et al. Cryoballoon or radiofrequency ablation for symptomatic paroxysmal atrial fibrillation: reintervention, rehospitalization, and quality-of-life outcomes in the FIRE AND ICE trial. Eur Heart J. 2016; Oct 7;37(38): 2235-2245

Low incidence of adverse events

Similar between energy sources

FIRE AND ICE Trial: Cryoballoon Met Non-Inferiority Safety Endpoint¹

Primary safety endpoint results:

RFC group 51 vs. Cryoballoon group 40 (HR = 0.78:95% CI = 0.52-1.18; p = 0.24) One-year Kaplan-Meier event rate estimates: 10.2% Cryoballoon and 12.8% RFC



Profile:

Although not statistically significant, there was a trend towards greater groin site complications, atrial flutter/atrial tachycardia and cardiac tamponade with radiofrequency. While there were significantly more PNI unresolved at discharge with cryoballoon

*Includes vascular pseudoaneurysm, AV fistula, device-related infection, hematoma, puncture site hemorrhage, groin pain. ? Adjudicated as a serious (e.g., hospitalization) and casually related to the therapeutic intervention (e.g., ablation-induced or drug-induced) ** 0.5% PNI ongoing after 3 months. 1 Kuck KH, et al. Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. N Engl J Med. 2016; 374(23):2235-2245

First-line Ablation for the Treatment of Atrial Fibrillation

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