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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Cryoballoon Ablation as Initial Treatment for Atrial Fibrillation

JACC State-of-the-Art Review

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ABSTRACT

Atrial fibrillation (AF), the most common sustained arrhythmia observed in clinical practice, is a chronic and progressive disorder characterized by exacerbations and remissions. Guidelines recommend antiarrhythmic drugs as the initial therapy for the maintenance of sinus rhythm; however, antiarrhythmic drugs have modest efficacy to maintain sinus rhythm and can be associated with significant adverse effects. An initial treatment strategy of cryoballoon catheter ablation in patients with treatment-naïve AF has been shown to significantly improve arrhythmia outcomes (freedom from any, or symptomatic atrial tachyarrhythmia), produce clinically meaningful improvements in patient-reported outcomes (symptoms and quality of life), and significantly reduce subsequent health care resource use (hospitalization), and it does not increase the risk of serious or any adverse events compared with initial antiarrhythmic drug therapy. These findings are relevant to inform patients, providers, and health care systems regarding the initial choice of rhythm-control therapy in patients with treatment-naïve AF. (J Am Coll Cardiol 2021;78:914–930) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Atrial fibrillation (AF), the most common sustained arrhythmia observed in clinical practice, is a chronic and progressive disorder characterized by exacerbations and remissions. Although arrhythmia suppression is desirable, the contemporary goals of AF management are centered on symptom relief, improvement in quality of life, reduction in morbidity, and reduction in AF-related health care resource use (eg, emergency department visits and hospitalization) (1).

Without treatment, atrial fibrillation will recur within a year in up to 75% of patients after a first episode (2-4). Contemporary guidelines recommend antiarrhythmic drugs as the initial therapy for the maintenance of sinus rhythm (5-7). However, antiarrhythmic drugs have modest efficacy at maintaining sinus rhythm and are associated with short- and long-term adverse effects (8). Catheter ablation for AF, which is centered on electrical isolation of triggering foci within the pulmonary veins, has been shown in

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HIGHLIGHTS

- Compared with antiarrhythmic drug therapy, a strategy of initial cryoballoon ablation reduces arrhythmia recurrence without increasing the risk of adverse events.
- Successful cryoballoon ablation improves quality of life for patients with AF.
- Further studies are needed to guide optimum selection of patients for cryoballoon ablation as the initial rhythm control strategy for patients with AF and to assess the economic value of this approach over initial antiarrhythmic drug therapy.

multiple large observational studies and randomized controlled trials to be superior to antiarrhythmic drug therapy in maintaining sinus rhythm when antiarrhythmic drugs have been ineffective, are contraindicated, or cause intolerable adverse effects (9).

It has been postulated that earlier intervention with catheter ablation (ie, as an initial therapy prior to antiarrhythmic drugs) may impart clinical benefits. Although prior studies of first-line catheter ablation with radiofrequency energy have been inconclusive (10-12), 3 multicenter randomized trials have recently compared initial rhythm control with cryoballoon catheter ablation vs antiarrhythmic drug therapy in patients with symptomatic, treatment-naïve, paroxysmal atrial fibrillation (13-15). The scope of this paper is to review the rationale and evidence supporting an early invasive approach to atrial fibrillation, with a specific focus on cryoballoon-based catheter ablation.

IMPACT OF AF

AF is the most common sustained arrhythmia encountered in clinical practice, with a prevalence in the range of 1%-2% of the general population, which increases significantly with age (<1.0% at 50 years, to 4% at 65 years, and 12% at 80 years) (1). Although rarely acutely life-threatening, AF is associated with significant impairments in functional capacity and quality of life, with a degree of impairment that is comparable or worse than in patients with heart failure or coronary disease, and with metrics of illness intrusiveness comparable to chronic hemodialysis (16,17). Left unchecked, AF is independently associated with an up to 5-fold increased risk of thromboembolism and an up to 4-fold increased risk of mortality (18,19).

Given the combination of disease prevalence and the magnitude of symptomatic impairment, the economic burden of AF is substantial. Depending on the jurisdiction, it has been estimated that AF is responsible for up to 2.5% of annual health care expenditures, with the majority of these expenditures attributed to the direct costs associated with the provision of acute care (eg, arrhythmia-related emergency department visits and hospital admissions) (20,21). In absolute terms, in the United States, AF resulted in 276,000 emergency department visits, 350,000 hospitalizations, 234,000 hospital outpatient visits, and 5 million outpatient office visits in 2001 (22). The annual financial impact to the health care system has been estimated to be $8.85 billion (adjusted to 2020 U.S. dollars [USD]), of which $3.83 billion has been attributed to the hospital charges and procedures for which AF was the principal diagnosis, $2.57 billion attributed to the incremental inpatient costs associated with AF as a comorbid diagnosis, $2.03 billion for ambulatory/outpatient treatment of AF, and $353 million for prescription drug costs (22). On a per-patient basis, the direct annual cost of AF has been estimated to be $22,462 (2020 USD) per AF patient compared with $5,518 (adjusted 2020 USD) for those without AF, leading to an excess annual direct cost of $16,944-$19,529 (adjusted 2020 USD) (23,24).

Unfortunately, despite advances in management, the acute care burden associated with AF is increasing, with these direct costs being forecast to increase to more than 4% of annual health care expenditures over the next 2 decades (20,25). As such, significant benefits would be expected from management strategies that meaningfully reduce the symptomatic impact of AF, the direct costs caused by health care use, and the indirect costs associated with lost productivity (eg, caused by days of work missed because of illness).

ABBREVIATIONS AND ACRONYMS

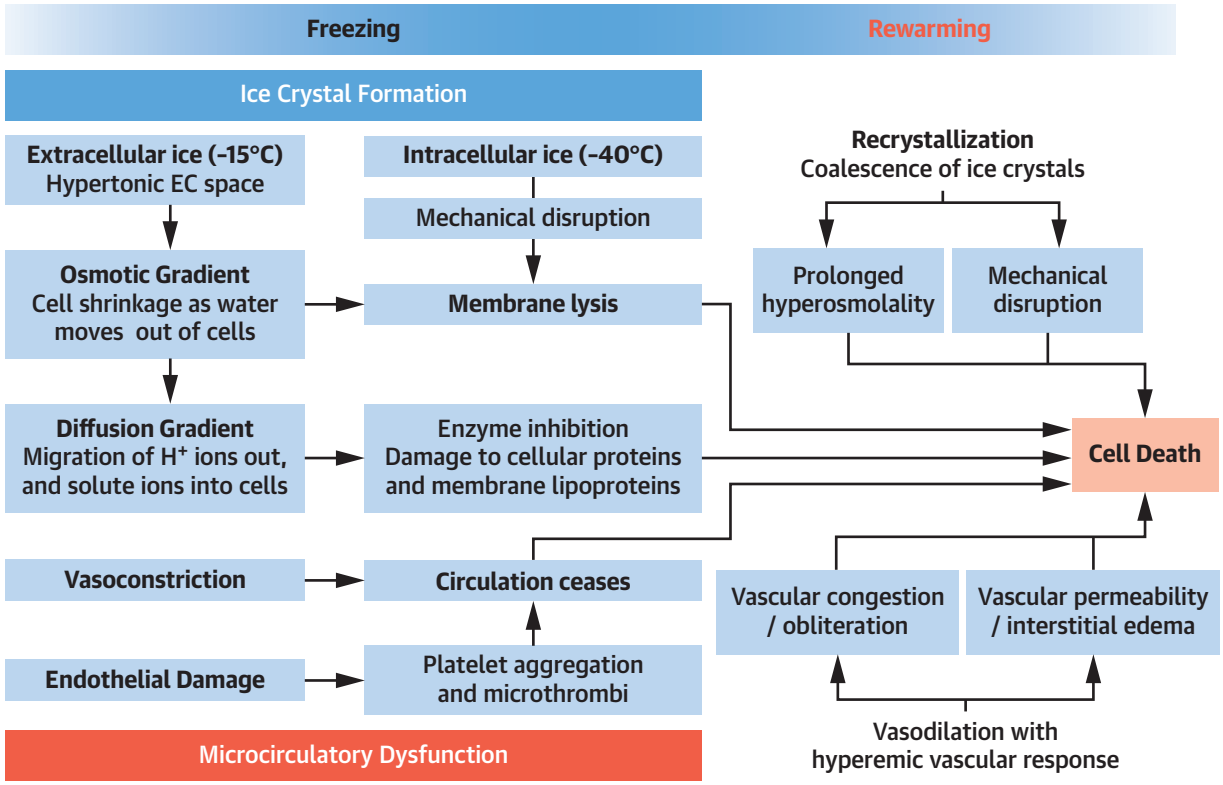
AF = atrial fibrillation

USD = United States dollars

EARLY MANAGEMENT OF AF

AF is a chronic progressive disease characterized by exacerbations and remissions. Early in its course, AF is predominantly triggered by repetitive rapid discharges originating from the pulmonary veins, and is perpetuated via micro-re-entrant circuits around the pulmonary venous-left atrial junction and within the atrial body (1). Early in its course, AF is predominantly an isolated electrical disorder; however, the effect of the intermittent AF episodes is cumulative, resulting in electrical, contractile, and structural remodeling of the atria. This change gives rise to a greater predisposition toward sustained arrhythmia,

FIGURE 1 Lesion Formation With Cryothermal Ablation



Cryoablation leads to cellular injury caused by a combination of ice crystal–induced osmotic stress, with subsequent membrane lysis and enzyme inhibition **(left top)**, as well as ischemic cell death caused by microcirculatory failure **(left bottom)**. Rewarming exacerbates this injury caused by ice crystal coalescence **(right top)** and hyperemic vascular response **(bottom right)**. EC = extracellular; H^+ = hydrogen ion; IC = intracellular.

driving the progression from paroxysmal self-terminating AF to persistent forms of AF that require intervention for termination (eg, cardioversion) (3,26). This progression from paroxysmal to persistent forms of AF has been associated with increasing rates of myocardial infarction, thromboembolism, and heart failure (27).

The recently-published EAST-AFNET 4 (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial) has highlighted the role of early rhythm control for patients with newly diagnosed (≤1 year) AF (28). Specifically, compared with an initial rate-control strategy, early rhythm control (predominantly using Class Ic antiarrhythmic drugs, amiodarone and dronedarone) significantly reduced the composite primary outcome of cardiovascular death, stroke, and hospitalization for worsening heart failure and acute coronary syndrome (HR: 0.79; 95% CI: 0.66-0.94). This translated to approximately 1 less composite primary outcome per year of treatment with early rhythm control versus a rate-control strategy. Importantly, all components of the composite outcome favored early rhythm control, with significant reductions in death from cardiovascular causes (HR: 0.72; 95% CI: 0.52-0.98) and stroke (HR: 0.65; 95% CI: 0.44-0.97). These findings are in contradistinction to the concept of rate control borne out in large clinical trials performed decades prior (that enrolled patients further along in their AF course) and provided reasonable justification to pursue early rhythm control in patients with a recent diagnosis of AF (28).

Contemporary guidelines recommend antiarrhythmic drugs as the initial therapy for the maintenance of sinus rhythm (5-7). Specifically, the major North American and European society guidelines provide only a conditional recommendation for AF ablation as first-line therapy, reserving it for highly selected patients with symptomatic paroxysmal (Class IIa in European Society of Cardiology and American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines) or persistent AF (Class IIb in European Society of Cardiology and

TABLE 1 Study Characteristics

	Cryo-FIRST	EARLY-AF	STOP-AF First
Design	Prospective, multicenter, randomized	Prospective, multicenter, randomized	Prospective, multicenter, randomized
Setting (number of centers)	Australia, Europe, Latin America (20)	Canada (18)	United States (24)
Enrollment	2014-2018	2017-2018	2017-2019
Blanking period	90 days from cryoablation procedure or AAD initiation	90 days from cryoablation procedure or AAD initiation	90 days from cryoablation procedure or AAD initiation
Follow-up duration	12 months	12 months	12 months
Primary outcome	Any recurrence of atrial tachyarrhythmia (AF, AT, AFL) lasting longer than 30 seconds	Any recurrence of atrial tachyarrhythmia (AF, AT, AFL) lasting longer than 30 seconds	Any recurrence of atrial tachyarrhythmia (AF, AT, AFL) lasting longer than 30 seconds
Key secondary outcomes	• Quality of life (AFEQT) • Symptoms • Health care use • Adverse events	• Quality of life (AFEQT, EQ5D) • Symptoms • Health care use • Adverse events	• Quality of life (AFEQT) • Health care use • Adverse events

AF = atrial fibrillation; AFEQT = Atrial Fibrillation Effect on QualiTy-of-life; AFL = atrial flutter; AT = atrial tachycardia; Cryo-FIRST = Catheter Cryoablation Versus Antiarrhythmic Drug as First-Line Therapy of Paroxysmal Atrial Fibrillation; EARLY-AF = Early Aggressive Invasive Intervention for Atrial Fibrillation; STOP-AF First = Cryoballoon Catheter Ablation in an Antiarrhythmic Drug Naive Paroxysmal Atrial Fibrillation.

American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines) without major risk factors for recurrence, and considering patient preference, benefit, and risk (5,6). The Canadian Cardiovascular Society guidelines provide a "weak" recommendation for first-line catheter ablation in select patients with symptomatic AF, with no distinction between paroxysmal or persistent AF (7).

Although antiarrhythmic drugs have been proven to be more effective than placebo and remain the

TABLE 2 Patient Characteristics

	Cryo-FIRST		EARLY-AF		STOP-AF First	
	Cryoablation	AAD	Cryoablation	AAD	Cryoablation	AAD
Randomized	107	111	154	149	108	102
Included in analysis	107	111	154	149	104	99
Baseline demographics						
Mean age, y	50.5	54.1	57.7	59.5	60.4	61.6
Male	76 (71)	72 (65)	112 (73)	102 (68)	63 (61)	57 (58)
Paroxysmal AF	107 (100)	111 (100)	147 (96)	140 (94)	104 (100)	99 (100)
Mean time since AF diagnosis, y	0.7	0.8	Median 1.0	Median 1.0	1.3	1.3
AFEQT, mean	62.0	59.9	61.4	57.4	58.5	62.9
CHA_2DS_2-VASc score, mean			1.9	1.9		
0/1	82 (77)	78 (70)	68 (44)	65 (44)	48 (46)	44 (44)
2	13 (12)	15 (14)	53 (34)	48 (32)	33 (32)	19 (19)
≥3	7 (7)	12 (11)	33 (21)	36 (24)	23 (22)	26 (26)
Comorbidities						
Hypertension	33 (31)	40 (36)	57 (37)	55 (37)	58 (54)	57 (56)
Ischemic heart disease	2 (2)	1 (1)	12 (8)	7 (5)	13 (12)	12 (12)
Heart failure	0 (0)	0 (0)	14 (9)	14 (9)	1 (1)	3 (3)
Previous stroke/TIA	0 (0)	1 (1)	4 (3)	5 (3)	2 (2)	3 (3)
Mean LVEF, %	62.8	63.7	59.6	59.8	60.9	61.1
Left atrial diameter, mm	37.0	38.0	39.5	38.1	38.7	38.2
Baseline medications						
Oral anticoagulant	38 (36)	49 (46)	103 (67)	96 (64)	72 (69)	68 (69)
Beta-blocker	54 (50)	56 (50)	85 (55)	92 (62)	6 (6)	9 (9)
Nondihydropyridine calcium-channel blocker	9 (8)	15 (14)	11 (7)	10 (7)	10 (10)	4 (4)
Previous use of class I or III AAD			40 (26)	44 (30)		

Values are n or n (%), unless otherwise indicated.

AAD = antiarrhythmic drug; LVEF = left ventricular ejection fraction; TIA = transient ischemic attack; other abbreviations as in Table 1.

TABLE 3 Rhythm Monitoring Protocols and Arrhythmia Detection

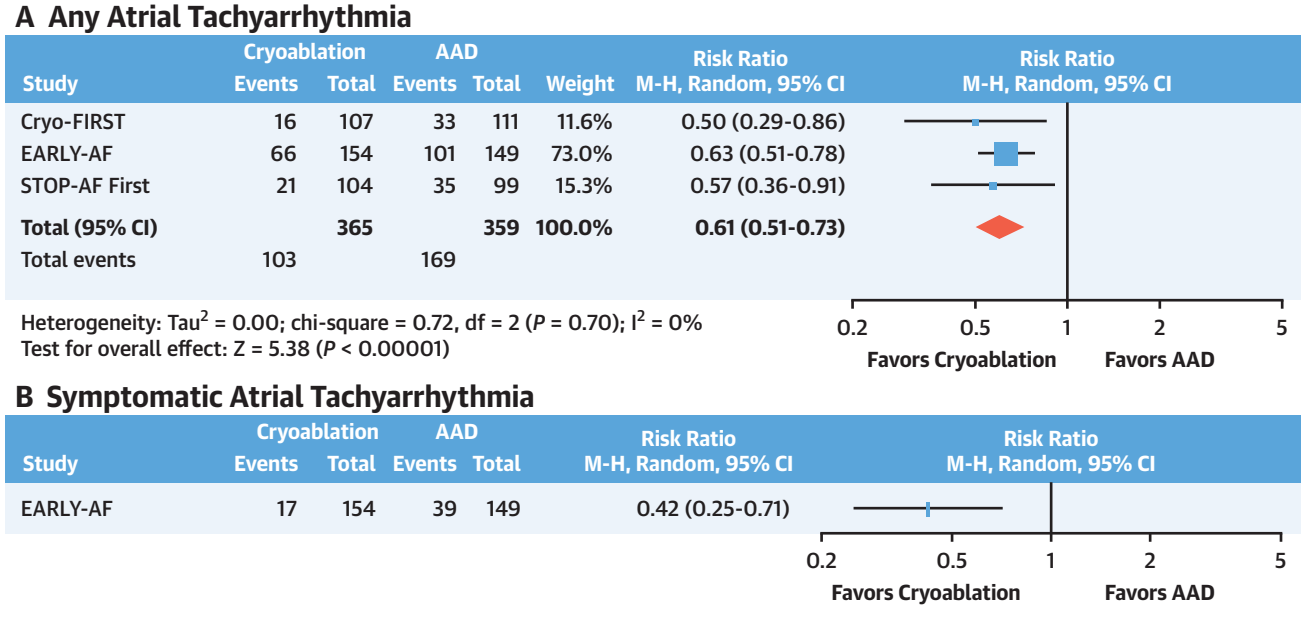
	Cryo-FIRST	EARLY-AF	STOP-AF First
Primary outcome	Any recurrence of atrial tachyarrhythmia (AF, AT, AFL) lasting longer than 30 seconds	Any recurrence of atrial tachyarrhythmia (AF, AT, AFL) lasting longer than 30 seconds	Any recurrence of atrial tachyarrhythmia (AF, AT, AFL) lasting longer than 30 seconds
Monitoring protocol and adherence	7-day Holter every 3 months (94% adherence)	Implantable loop recorder with daily transmissions (100% adherence)	24-h Holter at 6 and 12 months (87% adherence) Weekly patient-activated transtelephonic event recorder (81% adherence)
Freedom from documented atrial tachyarrhythmia	82.2% ablation 67.6% AAD	57.1% ablation 32.2% AAD	79.8% ablation 64.6% AAD
Absolute risk reduction	14.6%	24.9%	15.2%
Relative risk (95% confidence interval)	0.50 (0.29-0.86)	0.63 (0.51-0.78)	0.57 (0.36-0.91)

Abbreviations as in Tables 1 and 2.

"first-line" therapy for the maintenance of sinus rhythm, these medications have only modest efficacy at maintaining sinus rhythm (8,13). Moreover, antiarrhythmic drugs are associated with significant noncardiac side-effects, including end-organ toxicity and the potential for pro-arrhythmia (eg, a 3- to 4-fold increased propensity toward malignant ventricular arrhythmias) (8). In addition, the long-term use of sotalol and amiodarone has been associated with increased mortality (OR: 4.32; 95% CI: 1.59-11.70; $P = 0.013$; and OR: 2.73; 95% CI: 1.00-7.41; $P = 0.049$, respectively) (8).

Conversely, multiple observational studies and randomized controlled trials have demonstrated that catheter ablation is superior to drug therapy for sinus rhythm maintenance, symptomatic improvement, and enhancement in functional capacity and quality of life (9,29). Moreover, because catheter ablation is a tailored procedure designed to modify the pathogenic mechanism of AF initiation and perpetuation, it is thought that ablation may alter the trajectory of this chronic progressive disease. Building on observational evidence, the recently-published ATTEST (Catheter ablation or medical therapy to delay

FIGURE 2 Atrial Tachyarrhythmia Recurrence



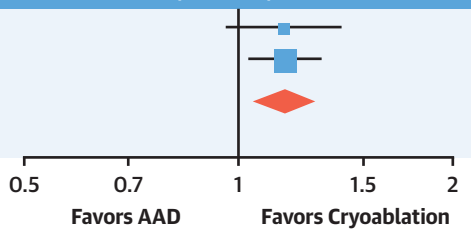
(A) Any atrial tachyarrhythmia. **(B)** Symptomatic atrial tachyarrhythmia.

FIGURE 3 Quality of Life

A Asymptomatic at 12 Months

Study	Cryoablation Events	Cryoablation Total	AAD Events	AAD Total	Weight	Risk Ratio M-H, Random, 95% CI
Cryo-FIRST	77	107	69	111	28.3%	1.16 (0.96-1.40)
EARLY-AF	131	154	109	149	71.7%	1.16 (1.03-1.31)
Total (95% CI)		**261**		**260**	**100.0%**	**1.16 (1.05-1.28)**
Total events	208		178			

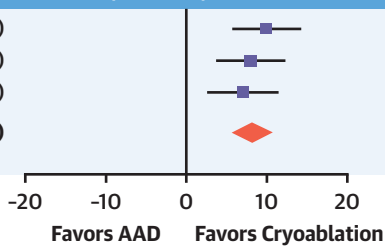
Heterogeneity: Tau^2 = 0.00; chi-square = 0.00, df = 1 (P = 0.97); I^2 = 0%
Test for overall effect: Z = 2.94 (P = 0.003)



B Mean Difference in AFEQT Score

Study	Cryoablation Mean	Cryoablation SD	Cryoablation Total	AAD Mean	AAD SD	AAD Total	Weight	Mean Difference IV, Random, 95% CI
Cryo-FIRST	88	14.8	89	78.1	14.8	92	33.7%	9.90 (5.59-14.21)
EARLY-AF	88.3	19.1	154	80.3	19.1	149	33.9%	8.00 (3.70-12.30)
STOP-AF First	91.9	15.4	99	84.9	15.4	90	32.4%	7.00 (2.60-11.40)
Total (95% CI)			**342**			**331**	**100.0%**	**8.32 (5.81-10.82)**

Heterogeneity: Tau^2 = 0.00; chi-square = 0.88, df = 2 (P = 0.64); I^2 = 0%
Test for overall effect: Z = 6.51 (P < 0.00001)



(A) Likelihood of being asymptomatic at 12 months. **(B)** Mean difference in AFEQT (Atrial Fibrillation Effect on QualiTy-of-life) score at 12 months between randomized groups. Analyses were calculated based on the adjusted mean difference and 95% confidence interval/standard error. Standard deviations presented for the randomized groups were calculated from the standard error for differences in means assuming homogeneity of variance.

progression of atrial fibrillation) trial demonstrated that catheter ablation was superior to guideline-directed antiarrhythmic drug therapy in delaying the progression from paroxysmal to persistent AF (2.4% [95% CI: 0.6%-9.4%] vs 17.5% [95% CI, 10.7-27.8%] progression at 3 years of follow-up; 1-sided P = 0.0009) (26).

However, it is important to consider that the majority of catheter ablation studies performed to date have focused on patients where antiarrhythmic drugs were ineffective, contraindicated, or poorly tolerated. By design, these studies preselected a population in whom antiarrhythmic drugs have proven to be ineffectual, weighting the therapeutic benefit significantly toward ablation (eg, selection bias). Although it has been postulated that early invasive intervention with catheter ablation offers an opportunity to halt the progressive pathoanatomical changes associated with AF, it remained unknown whether the potential benefits of catheter ablation would be as substantial when delivered as a "first-line" therapy (eg, prior to medication failure) (26,30). As such there has been renewed interest in determining the most effective initial treatment for newly diagnosed AF, particularly in light of the favorable safety profile of contemporary AF ablation procedures (13-15,31-34).

STUDIES OF FIRST-LINE RADIOFREQUENCY ABLATION

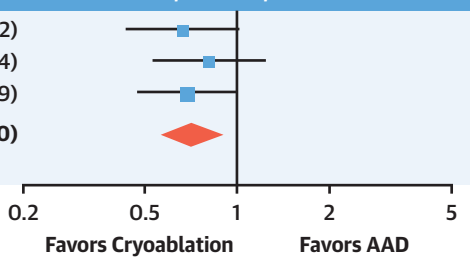
Previous studies have attempted to answer whether a population may exist whereby the effectiveness of the procedure would be sufficiently high, and the procedural risks sufficiently low that it would be appropriate to offer AF ablation as first-line therapy. These studies employing an initial catheter ablation strategy using radiofrequency energy have been limited by a failure to demonstrate a significant improvement in arrhythmia outcomes (10,11), high rates of cross-over between randomized groups (predominantly from antiarrhythmic drugs to ablation) (10-12), and high rates of repeat ablation procedures (10-12). Despite disparate ablation techniques, these 3 randomized studies demonstrated consistent but relatively low absolute success rates (45.5%-52.7% freedom from atrial tachyarrhythmia in the ablation arm vs 27.9%-

FIGURE 4 Forest Plot Reporting Health Care Resource Use

A Health Care Utilization

Study	Cryoablation Events	Cryoablation Total	AAD Events	AAD Total	Weight	Risk Ratio M-H, Random, 95% CI
Cryo-FIRST	25	107	39	111	30.2%	0.66 (0.43-1.02)
EARLY-AF	30	154	36	149	29.8%	0.81 (0.53-1.24)
STOP-AF First	31	104	43	99	39.9%	0.69 (0.47-0.99)
Total (95% CI)		**365**		**359**	**100.0%**	**0.71 (0.56-0.90)**
Total events	86		118			

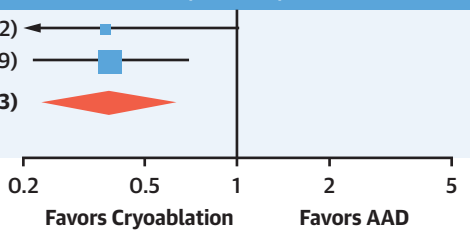
Heterogeneity: Tau^2 = 0.00; chi-square = 0.46, df = 2 (P = 0.79); I^2 = 0%
Test for overall effect: Z = 2.83 (P = 0.005)



B Hospitalization

Study	Cryoablation Events	Cryoablation Total	AAD Events	AAD Total	Weight	Risk Ratio M-H, Random, 95% CI
EARLY-AF	5	154	13	149	25.1%	0.37 (0.14-1.02)
STOP-AF First	13	104	32	99	74.9%	0.39 (0.22-0.69)
Total (95% CI)		**258**		**248**	**100.0%**	**0.38 (0.23-0.63)**
Total events	18		45			

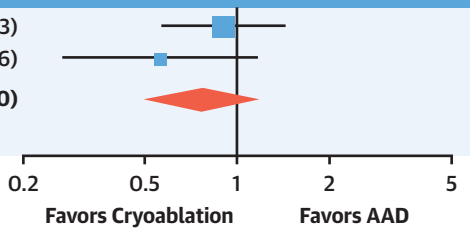
Heterogeneity: Tau^2 = 0.00; chi-square = 0.00, df = 1 (P = 0.95); I^2 = 0%
Test for overall effect: Z = 3.73 (P = 0.0002)



C Emergency Department Visit

Study	Cryoablation Events	Cryoablation Total	AAD Events	AAD Total	Weight	Risk Ratio M-H, Random, 95% CI
EARLY-AF	28	154	30	149	68.2%	0.90 (0.57-1.43)
STOP-AF First	10	104	17	99	31.8%	0.56 (0.27-1.16)
Total (95% CI)		**258**		**248**	**100.0%**	**0.78 (0.50-1.20)**
Total events	38		47			

Heterogeneity: Tau^2 = 0.02; chi-square = 1.17, df = 1 (P = 0.28); I^2 = 15%
Test for overall effect: Z = 1.14 (P = 0.25)



(A) Any health care use, **(B)** hospitalization >24 hours, **(C)** emergency department consultation, **(D)** cardioversion, and **(E)** nonprotocol ablation (defined as repeat ablation in patients randomized to first-line cryoablation, or "cross-over" ablation performed in those randomized to antiarrhythmic drug therapy).

Continued on the next page

43.9% in the antiarrhythmic drug arm) (10-12). In aggregate, the relative benefit of first-line radiofrequency ablation was limited (relative risk [RR]: 0.81 for any arrhythmia; 95% CI: 0.68-0.96; P = 0.01) (Supplemental Figure 3) or nonsignificant (RR: 0.62 for symptomatic arrhythmia; 95% CI: 0.38-1.01; P = 0.06) (Supplemental Figure 4), which, when combined with the lack of procedural standardization and inconsistent procedural endpoints, have limited the impact of these studies (10-12). In addition, the outcomes of focal point-by-point radiofrequency catheter ablation are highly dependent on operator competency given the inherent difficulties associated with creating contiguous curvilinear ablation lesions using techniques originally developed for focal arrhythmic sources (35).

CRYOBALLOON ABLATION MECHANISMS AND POTENTIAL COMPLICATIONS

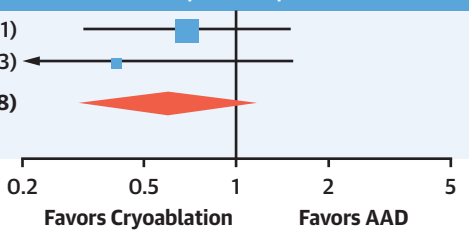
Given these known limitations considerable effort has been directed toward developing technologies to achieve safer and more effective pulmonary vein isolation that is less reliant on operator dexterity. One such system is the Arctic Front Cryoballoon (Medtronic CryoCath). The cryoballoon system consists of a

FIGURE 4 Continued

D Cardioversion

Study	Cryoablation Events	Cryoablation Total	AAD Events	AAD Total	Weight	Risk Ratio M-H, Random, 95% CI
EARLY-AF	10	154	14	149	74.3%	0.69 (0.32-1.51)
STOP-AF First	3	104	7	99	25.7%	0.41 (0.11-1.53)
Total (95% CI)		**258**		**248**	**100.0%**	**0.60 (0.31-1.18)**
Total events	13		21			

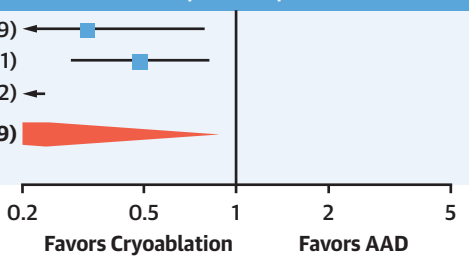
Heterogeneity: $Tau^2 = 0.00$; chi-square = 0.45, df = 1 ($P = 0.50$); $I^2 = 0\%$
Test for overall effect: Z = 1.47 ($P = 0.14$)



E Nonprotocol Ablation

Study	Cryoablation Events	Cryoablation Total	AAD Events	AAD Total	Weight	Risk Ratio M-H, Random, 95% CI
Cryo-FIRST	6	107	19	111	39.8%	0.33 (0.14-0.79)
EARLY-AF	18	154	36	149	45.0%	0.48 (0.29-0.81)
STOP-AF First	0	104	34	99	15.2%	0.01 (0.00-0.22)
Total (95% CI)		**365**		**359**	**100.0%**	**0.24 (0.06-0.89)**
Total events	24		89			

Heterogeneity: $Tau^2 = 0.92$; chi-square = 9.54, df = 2 ($P = 0.008$); $I^2 = 79\%$
Test for overall effect: Z = 2.13 ($P = 0.03$)



steerable 10.5-F catheter with distally mounted polyurethane and polyester balloons specifically designed to achieve pulmonary venous isolation (PVI) with a single ablation lesion. It is introduced to the left atrium via a 15-F deflectable delivery sheath and connected to an external console, which houses the cryorefrigerant. This cryorefrigerant is delivered to the distal aspect of the inner balloon via an ultrafine injection tube, where the refrigerant is pressurized through a restriction tube before undergoing a liquid-to-gas phase change as it enters the distal aspect of the inner balloon. The cryorefrigerant returns to the console through a central lumen maintained under vacuum.

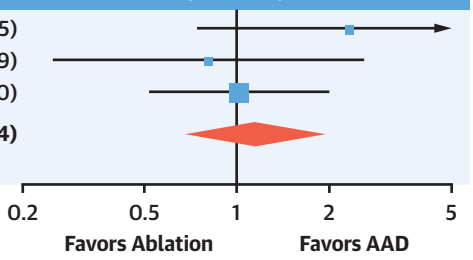
In contrast to radiofrequency energy, lesion formation with cryothermal ablation occurs through convective cooling, whereby the cryorefrigerant absorbs heat from the tissue surrounding the catheter (**Figure 1**). This process results in cold-induced cellular injury caused by a combination of: 1) direct freezing-induced cellular damage secondary to extracellular ice crystal formation and osmotic stress; and 2) ischemic cell death caused by microcirculatory failure (36,37). The induction of freezing results in progressive hypothermia results in slowing of cellular metabolism, loss of ion pump transport, and a more acidic intracellular pH (38). Continued cooling results in the formation of extracellular ice crystals, which triggers extracellular hypertonia with a compensatory egress of water from the intracellular space in order to re-establish osmotic equilibrium (39-41). This newly established osmotic gradient precipitates a diffusion gradient between the extracellular and intracellular spaces, resulting in the net movement of H^+ ions out of the cell and the migration of solute ions into the cell, which further reduces intracellular pH and results in biochemical injury to the mitochondria, cellular protein damage, enzyme impairment, and adverse effects on plasma membrane lipoproteins (41,42). Following the freezing phase, there is coalescence of the intracellular and extracellular ice crystals, which increases the osmotic damage and generates shear forces that further disrupt the tissue architecture (40,43). In addition, the restoration of microcirculation during rewarming is associated with vascular obliteration caused by interstitial edema (hyperemic vascular response and increased capillary permeability), endothelial-injury induced platelet aggregation, and microthrombi formation, resulting in extension of the tissue destruction through ischemic cellular necrosis (38,39,44). The final phase of tissue injury consists of reactive inflammation, followed by tissue repair and replacement fibrosis. Over several weeks there is generation of a mature

FIGURE 5 Safety Outcomes

A Serious Adverse Event

Study	Cryoablation Events	Cryoablation Total	AAD Events	AAD Total	Weight	Risk Ratio M-H, Random, 95% CI
Cryo-FIRST	9	107	4	111	20.6%	2.33 (0.74-7.35)
EARLY-AF	5	154	6	149	19.9%	0.81 (0.25-2.59)
STOP-AF First	15	104	14	99	59.5%	1.02 (0.52-2.00)
Total (95% CI)		**365**		**359**	**100.0%**	**1.15 (0.69-1.94)**
Total events	29		24			

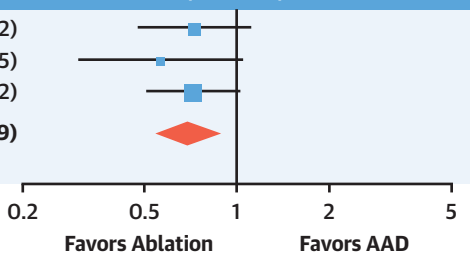
Heterogeneity: Tau^2 = 0.00; chi-square = 1.95, df = 2 (P = 0.38); I^2 = 0%
Test for overall effect: Z = 0.54 (P = 0.59)



B Any Safety Endpoint

Study	Cryoablation Events	Cryoablation Total	AAD Events	AAD Total	Weight	Risk Ratio M-H, Random, 95% CI
Cryo-FIRST	26	107	37	111	33.9%	0.73 (0.48-1.12)
EARLY-AF	14	154	24	149	16.0%	0.56 (0.30-1.05)
STOP-AF First	34	104	45	99	50.1%	0.72 (0.51-1.02)
Total (95% CI)		**365**		**359**	**100.0%**	**0.70 (0.54-0.89)**
Total events	74		106			

Heterogeneity: Tau^2 = 0.00; chi-square = 0.53, df = 2 (P = 0.77); I^2 = 0%
Test for overall effect: Z = 2.88 (P = 0.004)



(A) Treatment-related serious adverse events (as defined in the original study). **(B)** Any safety endpoint.

lesion, which has a distinct, well-circumscribed central region of dense cold-induced fibrosis surrounded by a narrow border of cellular death caused by microvascular injury and apoptosis (45).

Cryothermal energy offers several advantages when compared with radiofrequency energy, including: 1) freeze-mediated catheter adhesion, which facilitates catheter stability in challenging regions, such as the ridge between the left atrial appendage and pulmonary veins; 2) a well-demarcated homogeneous lesion that is thought to be more durable and less arrhythmogenic than the indistinct lesions associated with radiofrequency ablation; 3) minimal endocardial surface disruption, which is less thrombogenic than the lesions produced with radiofrequency energy (45); and 4) preservation of ultrastructural tissue integrity which may lead to reduced risk of complications such as cardiac perforation, esophageal injury, and pulmonary valve stenosis.

From a clinical perspective, the cryoballoon yields durable isolation of the arrhythmogenic muscular pulmonary venous sleeves as well as the antral pulmonary venous region responsible for arrhythmia perpetuation (46). Despite differing operator skillsets, cryoballoon ablation is associated with a high acute procedural success rate (>98% of patients achieving complete PVI) and long-term freedom from recurrent AF, with low rates of repeat ablation procedures (47). Moreover, cryoballoon ablation appears to be associated with a significantly lower risk of serious complication when compared to radiofrequency ablation, which is mostly due to a significantly lower incidence of pericardial effusion (0.8% cryoballoon vs 2.1% radiofrequency; OR: 0.44; 95% CI: 0.28-0.69; $P < 0.01$) and tamponade (0.4% cryoballoon vs 1.4% radiofrequency; OR: 0.31; 95% CI: 0.15-0.64; $P < 0.01$) (48,49). In contrast, cryoballoon ablation is associated with a significantly greater incidence of phrenic nerve injury (1.7% cryoballoon vs 0.0% radiofrequency; OR: 7.40; 95% CI: 2.56-21.34; $P < 0.01$) (48), which is thought to be caused by cold-induced large axonal loss (50). Interestingly, despite the requirement for a larger deflectable sheath with cryoballoon, there does not appear to be a significant difference in the incidence of vascular complications (1.1% cryoballoon vs 1.3% radiofrequency; OR: 0.79; 95% CI: 0.38-1.62; $P = 0.52$, 7 studies; n = 3,264). Last, studies have suggested that cryoballoon

ablation procedures are more reproducible. In contrast to radiofrequency ablation, where procedural outcomes are closely related to operator and center volumes, the outcomes following cryoballoon ablation are similar when performed in low- and high-volume centers and by low- and high-volume operators (35). This balance of generalizability, safety, and efficacy suggests that cryoballoon ablation may be a preferred toolset for initial (eg, first-line) ablation.

OVERVIEW OF STUDIES OF FIRST-LINE CRYOBALLOON ABLATION

Recently, 3 randomized controlled trials compared cryoballoon ablation to antiarrhythmic drugs as first-line therapy of AF: the Cryo-FIRST (Catheter Cryoablation Versus Antiarrhythmic Drug as First-Line Therapy of Paroxysmal Atrial Fibrillation) trial (15,51), the EARLY-AF (Early Aggressive Invasive Intervention for Atrial Fibrillation) trial (13), and the STOP-AF First (Cryoballoon Catheter Ablation in an Antiarrhythmic Drug Naive Paroxysmal Atrial Fibrillation) trial (see Supplemental Methods for further details on the search strategy, and meta-analysis) (14).

These 3 randomized trials included a total of 724 patients in their intention-to-treat (13,15) or modified intention-to-treat populations (14) (Supplemental Table 1). Across the 3 studies, the mean age was 57.4 years, and 67% were men (**Tables 1 and 2**). The majority of included patients were relatively free of significant comorbidities and had normal left ventricular function and left atrial size. Despite being enrolled early in their disease course (median time from first AF diagnosis of 1 year, with 98% having paroxysmal AF), the majority of patients were highly symptomatic (mean AFEQT [Atrial Fibrillation Effect on QualiTy-of-life] score 60.1).

Although the populations were globally similar, significant differences were observed between studies in patient age (youngest in Cryo-FIRST, oldest in STOP-AF First), and the prevalence of hypertension (lowest in Cryo-FIRST, highest in STOP-AF First; $P < 0.001$), ischemic heart disease (lowest in Cryo-FIRST, highest in STOP-AF First; $P < 0.01$), and heart failure (lowest in Cryo-FIRST, highest in EARLY-AF; $P < 0.001$).

Median time from randomization to cryoballoon catheter ablation was 50 days (IQR: 41-64 days) in EARLY-AF, and 24 days (IQR: 16-28 days) in STOP-AF First. Three-minute freezes were protocolized in EARLY-AF, recommended in STOP-AF First, and left to operator discretion in Cryo-FIRST. Procedure duration was shortest in Cryo-FIRST (84 ± 29 minutes), intermediate in EARLY-AF (106 minutes [IQR: 89-131 minutes]), and longest in STOP-AF First (139 ± 74 minutes; $P < 0.0001$). Fluoroscopy time was similar amongst studies (16 ± 14 minutes in Cryo-FIRST, 18.2 ± 11.8 minutes in STOP-AF First, and 18.9 minutes [IQR: 12.6-27.0 minutes] in EARLY-AF; $P = 0.15$).

Class Ic antiarrhythmic drugs were the most prescribed drug used in the antiarrhythmic drug group (first agent prescribed in 92% in Cryo-FIRST, 82% in EARLY-AF, and 79% in STOP-AF First). In EARLY-AF, 30% of the antiarrhythmic drug group required multiple antiarrhythmic drug trials to achieve objective suppression of AF on implantable monitor. Subtherapeutic antiarrhythmic drug dosing was observed in 7% in Cryo-FIRST, 0% in EARLY-AF, and 21% in STOP-AF First, with 18%, 0%, and 12% permanently discontinuing the study drug, respectively. Crossover from antiarrhythmic drugs to ablation before the occurrence of a primary endpoint event occurred in 14% in Cryo-FIRST, 0% in EARLY-AF, and 15% in STOP-AF First.

FIRST-LINE CRYOBALLOON ABLATION AND RECURRENT ATRIAL TACHYARRHYTHMIA

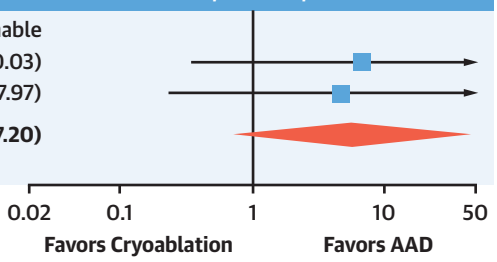
In contrast to prior studies of first-line radiofrequency ablation, first-line cryoballoon ablation demonstrated consistent and significant reductions in arrhythmia recurrence (13-15). When interpreting the absolute rates of arrhythmia recurrence, it is important to note that these 3 studies employed different arrhythmia monitoring protocols (**Table 3**). Noninvasive intermittent rhythm monitoring, such as that employed in the Cryo-FIRST and STOP-AF First trials, lacks sensitivity in detecting paroxysmal arrhythmia and may inflate the estimates of arrhythmia-free survival. However, because the monitoring strategy was applied consistently within studies, it is unlikely to affect the relative rates of recurrence between the within-study randomized groups. Specifically, despite apparent significant differences in the reported absolute success rates across the 3 studies (57.1%-82.2% freedom from atrial tachyarrhythmia in the ablation arm vs 32.2%-67.6% in the antiarrhythmic drug arm) the relative benefit of first-line cryoablation was remarkably consistent (13-15). In pooled analysis, initial treatment with cryoballoon ablation significantly reduced the risk of any recurrent atrial tachyarrhythmia compared with first-line antiarrhythmic drug therapy (RR: 0.61; 95% CI: 0.51-0.73), with a weighted absolute risk reduction of 19%, and a consistent treatment effect across the 3 randomized trials ($I^2 = 0\%$) (**Figure 2A**). Freedom from symptomatic atrial tachyarrhythmia

FIGURE 6 Serious Adverse Events

A Phrenic Nerve Injury

Study	Cryoablation Events	Cryoablation Total	AAD Events	AAD Total	Weight	Risk Ratio M-H, Random, 95% CI
Cryo-FIRST	0	107	0	111		Not estimable
EARLY-AF	3	154	0	149	51.2%	6.77 (0.35-130.03)
STOP-AF First	2	104	0	99	48.8%	4.76 (0.23-97.97)
Total (95% CI)		**365**		**359**	**100.0%**	**5.70 (0.69-47.20)**
Total events	5		0			

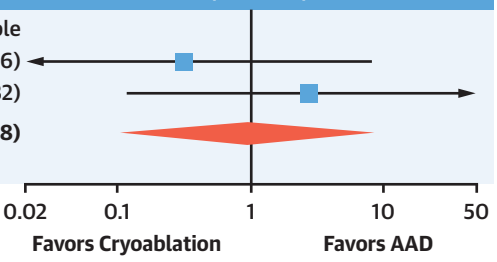
Heterogeneity: Tau^2 = 0.00; chi-square = 0.03, df = 1 (*P* = 0.87); I^2 = 0%
Test for overall effect: Z = 1.61 (*P* = 0.11)



B Pericardial Effusion or Tamponade

Study	Cryoablation Events	Cryoablation Total	AAD Events	AAD Total	Weight	Risk Ratio M-H, Random, 95% CI
Cryo-FIRST	0	107	0	111		Not estimable
EARLY-AF	0	154	1	149	49.9%	0.32 (0.01-7.86)
STOP-AF First	1	104	0	99	50.1%	2.86 (0.12-69.32)
Total (95% CI)		**365**		**359**	**100.0%**	**0.96 (0.10-9.18)**
Total events	1		1			

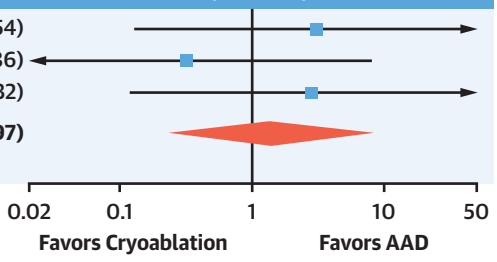
Heterogeneity: Tau^2 = 0.00; chi-square = 0.90, df = 1 (*P* = 0.34); I^2 = 0%
Test for overall effect: Z = 0.03 (*P* = 0.97)



C Stroke or Systemic Thromboembolism

Study	Cryoablation Events	Cryoablation Total	AAD Events	AAD Total	Weight	Risk Ratio M-H, Random, 95% CI
Cryo-FIRST	1	107	0	111	33.3%	3.11 (0.13-75.54)
EARLY-AF	0	154	1	149	33.3%	0.32 (0.01-7.86)
STOP-AF First	1	104	0	99	33.4%	2.86 (0.12-69.32)
Total (95% CI)		**365**		**359**	**100.0%**	**1.42 (0.23-8.97)**
Total events	2		1			

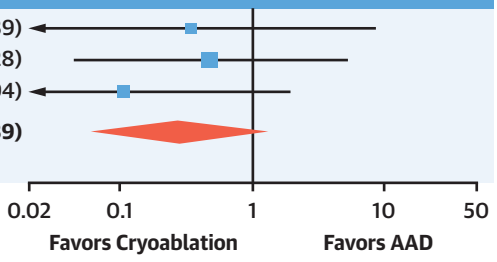
Heterogeneity: Tau^2 = 0.00; chi-square = 1.25, df = 2 (*P* = 0.54); I^2 = 0%
Test for overall effect: Z = 0.37 (*P* = 0.71)



D Syncope

Study	Cryoablation Events	Cryoablation Total	AAD Events	AAD Total	Weight	Risk Ratio M-H, Random, 95% CI
Cryo-FIRST	0	107	1	111	25.1%	0.35 (0.01-8.39)
EARLY-AF	1	154	2	149	44.7%	0.48 (0.04-5.28)
STOP-AF First	0	104	4	99	30.2%	0.11 (0.01-1.94)
Total (95% CI)		**365**		**359**	**100.0%**	**0.28 (0.06-1.39)**
Total events	1		7			

Heterogeneity: Tau^2 = 0.00; chi-square = 0.68, df = 2 (*P* = 0.71); I^2 = 0%
Test for overall effect: Z = 1.56 (*P* = 0.12)



(A) Phrenic nerve injury, **(B)** clinically significant pericardial effusion or tamponade, **(C)** stroke or systemic thromboembolism, **(D)** syncope, **(E)** bradycardia requiring pacemaker implantation, and **(F)** ventricular pro-arrhythmia.

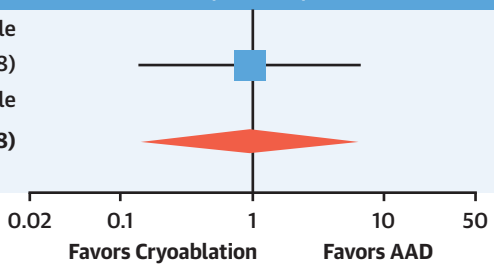
Continued on the next page

FIGURE 6 Continued

E Pacemaker Implantation

Study	Cryoablation Events	Cryoablation Total	AAD Events	AAD Total	Weight	Risk Ratio M-H, Random, 95% CI
Cryo-FIRST	0	107	0	111		Not estimable
EARLY-AF	2	154	2	149	100.0%	0.97 (0.14-6.78)
STOP-AF First	0	104	0	99		Not estimable
Total (95% CI)		**365**		**359**	**100.0%**	**0.97 (0.14-6.78)**
Total events	2		2			

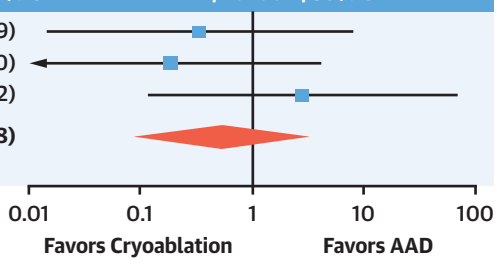
Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (*P* = 0.97)



F Ventricular Pro-Arrhythmia

Study	Cryoablation Events	Cryoablation Total	AAD Events	AAD Total	Weight	Risk Ratio M-H, Random, 95% CI
Cryo-FIRST	0	107	1	111	32.2%	0.35 (0.01-8.39)
EARLY-AF	0	154	2	149	35.7%	0.19 (0.01-4.00)
STOP-AF First	1	104	0	99	32.2%	2.86 (0.12-69.32)
Total (95% CI)		**365**		**359**	**100.0%**	**0.55 (0.09-3.38)**
Total events	1		3			

Heterogeneity: $Tau^2 = 0.00$; chi-square = 1.56, df = 2 (*P* = 0.46); $I^2 = 0\%$
Test for overall effect: Z = 0.64 (*P* = 0.52)



was only reported in EARLY-AF, where a significant 15.2% absolute reduction was observed (RR: 0.42; 95% CI: 0.25-0.71) (Figure 2B). Likewise, AF burden, or percentage time in AF, was significantly reduced with ablation (mean difference between ablation and antiarrhythmic drug groups of 3.3 ± 1.0%); however, burden data was only available in the EARLY-AF trial as it was the only study to employ the use of implantable cardiac monitors.

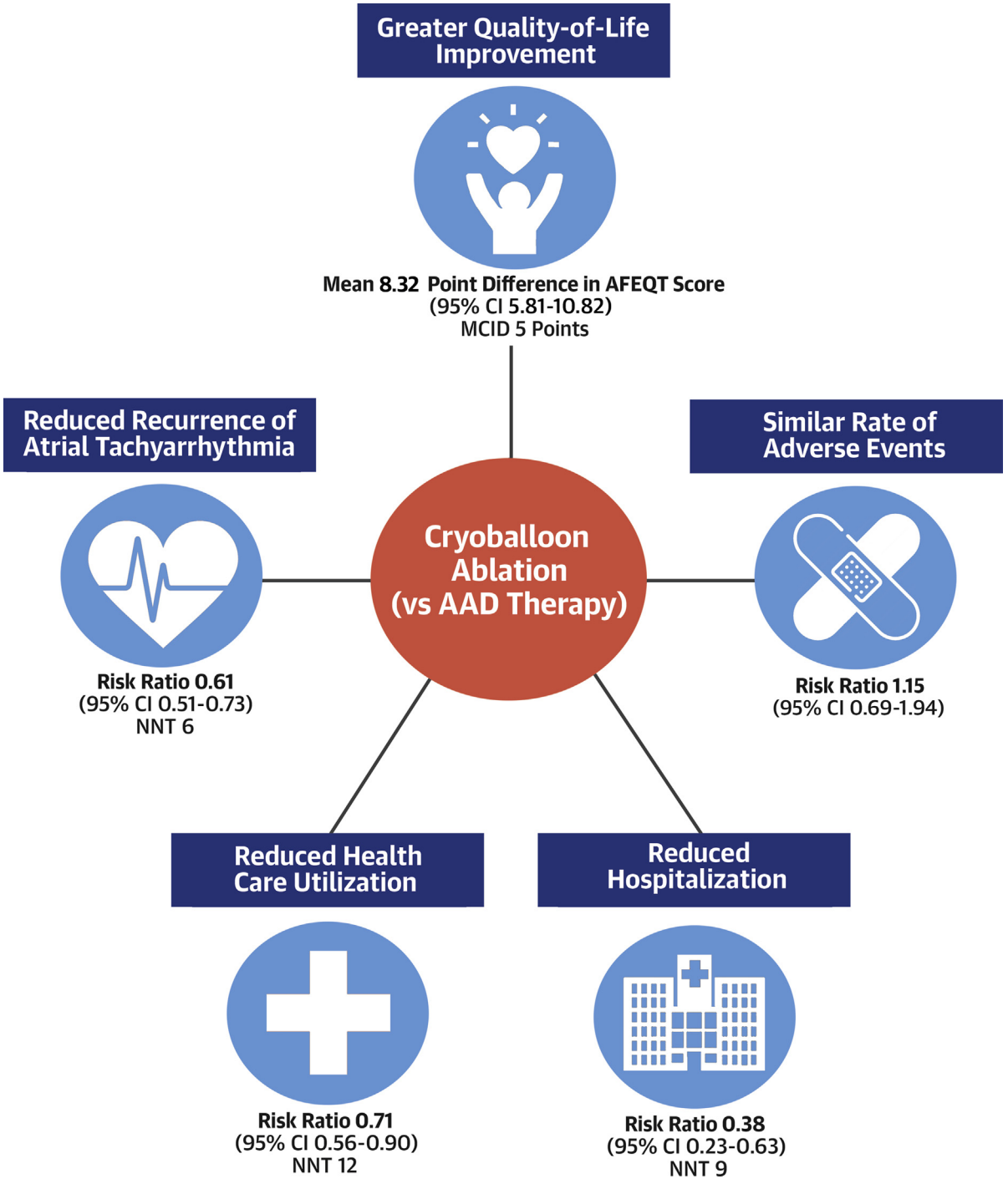
FIRST-LINE CRYOBALLOON ABLATION AND QUALITY OF LIFE

Although traditional outcome parameters, such as freedom from recurrent atrial tachyarrhythmia, are undoubtedly an important benchmark for clinical trials, this narrow focus is insufficient because it fails to the capture patient- and health system-level differences in treatment approaches. Specifically, a significant reduction in symptomatic AF episodes or symptoms related to AF may be considered a success from the patient or provider perspective, even in the presence documented recurrence of arrhythmia. The assessment of patient-reported outcomes with validated multidimensional instruments offers a complementary clinically relevant means to evaluate the impact of therapeutic interventions on patients' functional status and health.

Freedom from symptoms at 12 months was reported in Cryo-FIRST and EARLY-AF. In aggregate, patients treated with initial ablation were significantly more likely to be free of symptoms at 12 months of follow-up (80% with ablation vs 68% with antiarrhythmic drugs; RR: 1.16; 95% CI: 1.05-1.28; $I^2 = 0\%$; n = 521) (Figure 3A).

In addition, first-line cryoablation resulted in a significantly greater improvement in the disease-specific AFEQT quality-of-life score (mean 8.32-point difference between groups) compared with antiarrhythmic drug therapy (95% CI: 5.81-10.82; $I^2 = 0\%$; n = 673) (Figure 3B). The magnitude of improvement between randomized groups more than exceeded the established threshold for a clinically meaningful improvement, suggesting that clinical benefit is obtained in quality-of-life outcomes when ablation is performed as the initial rhythm-control treatment (52). Similar improvements using generic quality of life instruments were observed with first-line radiofrequency ablation in RAAFT-1 (Radiofrequency Ablation vs Antiarrhythmic Drugs as First-line Treatment of Symptomatic Atrial Fibrillation) and MANTRA-PAF (Medical ANtiarrhythmic Treatment or

CENTRAL ILLUSTRATION First-Line Cryoballoon Pulmonary Vein Isolation in Patients With Treatment-Naive Atrial Fibrillation



Andrade, J.G. et al. J Am Coll Cardiol. 2021;78(9):914–930.

Meta-analysis of the 3 randomized "first-line" trials demonstrates that initial cryoballoon ablation is associated with significant reductions in arrhythmia recurrence and health care use, and significant improvements in quality of life and symptom status when compared with initial antiarrhythmic drug therapy. AAD = antiarrhythmic drug; AFEQT = Atrial Fibrillation Effect on QualiTy-of-life; CI = confidence interval; MCID = minimal clinically important difference; NNT = number need to treat.

Radiofrequency Ablation in Paroxysmal Atrial Fibrillation), but not in RAAFT-2 (Radiofrequency Ablation vs Antiarrhythmic Drugs as First-Line Treatment of Paroxysmal Atrial Fibrillation) (10-12).

Given the lack of patient and physician blinding, it is impossible to exclude placebo effect as a contributor to the significant improvement in health-related quality of life observed with first-line cryoablation. It is possible that part of the improvement may be related to "treatment expectancy," whereby patients expect to achieve an improvement in quality of life on the basis of having undergone a medical intervention; however, the relatively consistent magnitude of benefit observed across these studies, along with consistency with other, "harder" endpoints, suggests that the contribution may be minor.

FIRST-LINE CRYOBALLOON ABLATION AND HEALTH CARE USE

Despite continued advances in AF management, the direct costs associated with hospitalization and the provision of acute care are forecast to increase from 1.0%-2.5% to more than 4% of annual health care expenditures within the next 2 decades (20,25). As such, management strategies that meaningfully affect arrhythmia-related health care use would be expected to confer significant benefits to patients and health care systems.

Although no study was individually powered for health care use endpoints, pooled analysis demonstrated that significantly fewer patients randomized to first-line cryoballoon ablation experienced the composite health care use outcome compared with patients who were randomized to initial antiarrhythmic drug therapy (RR: 0.71; 95% CI: 0.56-0.90), with a weighted absolute risk reduction of 9% and a consistent treatment effect across the 3 randomized trials (I^2 = 0%) (**Figure 4A**). This was driven by a significant reduction in hospitalization, which was significantly reduced with first-line ablation (RR: 0.38; 95% CI: 0.23-0.63; I^2 = 0%; weighted absolute risk reduction of 12%) (**Figure 4B**). Nonsignificant reductions in emergency department visits (RR: 0.78; 95% CI: 0.50-1.20; I^2 = 15%) (**Figure 4C**) and cardioversions (RR: 0.60; 95% CI: 0.31-1.18; I^2 = 0%) (**Figure 4D**) were also observed. Nonprotocol ablation procedures (repeat ablation in patients randomized to first-line cryoablation, or "cross-over" ablation performed in those randomized to antiarrhythmic drug therapy) occurred significantly less often in the first-line ablation group (RR: 0.24; 95% CI: 0.06-0.89) (**Figure 4E**), although there was substantial statistical heterogeneity (I^2 = 79%) caused by differences between trial protocols in how such procedures could be performed. Taken together, these findings suggest that first-line catheter cryoballoon ablation may confer significant monetary benefits owing to lower utilization of acute care and inpatient resources.

Although these findings are consistent with previous observational data suggesting that health care resource use decreases significantly following catheter ablation (30,53-55), a reduction in health care use was not observed in the randomized studies of first-line radiofrequency ablation (RR: 0.98; 95% CI: 0.64-1.50) (56). Moreover, because the rate of hospitalization and emergency department visits are known to be highest in the first 2 months following ablation, it is possible that the true impact of first-line cryoballoon catheter ablation on health care use may be underestimated, as these studies only followed patients for 12 months (30,57).

SAFETY OF FIRST-LINE CRYOBALLOON ABLATION

If ablation is to be used earlier in the management of AF, then a thorough evaluation of safety is necessary. Catheter ablation is known for significant periprocedural complications, with studies reporting major complications in approximately 5% of patients (9,58). This includes an approximate 0.2% incidence of stroke or transient ischemic attack, 0.8% incidence of pericardial effusion, 0.4% incidence of cardiac tamponade, 0.3% incidence of severe pulmonary vein stenosis, 1.5% incidence of groin complication, 1.5% incidence of phrenic nerve injury, and <0.05% incidence of esophageal fistula or death (49).

The 3 randomized first-line cryoballoon ablation trials demonstrated that the risk of treatment-related serious adverse events was comparable between first-line catheter ablation and antiarrhythmic drug therapy, with ablation being associated with a slightly lower risk of any adverse event. This result was consistent whether analyzed by the composite definition of serious adverse events employed within the randomized controlled trials (RR: 1.15; 95% CI: 0.69-1.94; I^2 = 0%) (**Figure 5A**), based on a composite of clinically significant adverse events (pericardial effusion or tamponade, phrenic nerve injury, stroke or systemic thromboembolism, syncope, bradycardia requiring pacemaker implantation, ventricular proarrhythmia; RR: 0.74; 95% CI: 0.35-1.56), or by the individual clinically significant adverse events (**Figure 6**). In contrast, the occurrence of any adverse

event was lower in the cryoballoon group (RR: 0.70; 95% CI: 0.54-0.89; $I^2 = 0\%$) (**Figure 5B**).

EXTRAPOLATION OF RESULTS

At this point, it remains unknown whether the contemporary outcomes of first-line catheter ablation are generalizable to other ablation energy sources or to patients with more advanced forms of AF, and whether the benefits observed at 1 year persist in the longer term. Although recent trials have suggested that the outcomes of contact-force radiofrequency ablation and cryoballoon ablation are similar (33,34), the previous studies of first-line radiofrequency ablation outlined in our review did not observe comparable benefits in terms of arrhythmia freedom, quality of life, and health care use. Moreover, it is unknown whether the results of these first-line ablation studies can be extrapolated to patients with more advanced forms of AF (eg, persistent AF) or AF in association with a structurally abnormal heart (eg, AF in association with cardiomyopathy), in whom ablation beyond the pulmonary veins may be necessary. Strictly speaking, these first-line ablation studies were centered on a pulmonary vein isolation procedure, which is the cornerstone of the invasive management of paroxysmal AF. Although it is known that pulmonary vein isolation is less successful in patients with persistent AF (relative to paroxysmal AF) (59,60), randomized studies have not demonstrated that additional ablation targeting regions outside of the left atrial-pulmonary venous junction (eg, linear left atrial lesions; left-atrial appendage or posterior wall isolation; or the ablation of ganglionated plexi, nonpulmonary valve triggers, or regions with complex fractionation) improves clinical outcomes (61). Although it is technically feasible to perform extrapulmonary ablation with the cryoballoon (eg, left atrial appendage isolation or posterior wall isolation) (62,63), it is important to recognize that more extensive ablation has the potential to cause harm through increased procedural duration and complexity, increased intraprocedural or postprocedural complications, or the induction of iatrogenic arrhythmias, factors that may influence the risk-benefit balance of a first-line ablation approach. Irrespective of these considerations, recent studies have demonstrated that the benefit of ablation relative to antiarrhythmic drug therapy is consistent and maintained with more advanced forms of AF (64). The upcoming RAAFT-3 (First Line Radiofrequency Ablation Versus Antiarrhythmic Drugs for Persistent Atrial Fibrillation Treatment; NCT04037397) trial will provide further clarity as to whether the results of first-line radiofrequency ablation can be applied to persistent AF patients.

SUMMARY

An initial treatment strategy of cryoballoon catheter ablation in patients with treatment-naïve atrial fibrillation significantly improved arrhythmia outcomes, produced clinically meaningful improvements in patient-reported outcomes (eg, symptoms and quality of life), significantly reduced subsequent health care resource use, and did not increase the risk of adverse events compared with initial antiarrhythmic drug therapy (**Central Illustration**). These findings are relevant to inform patients, providers, and health care systems regarding the initial choice of rhythm-control therapy in patients with treatment-naive AF.

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KEY WORDS ablation, antiarrhythmic drugs, atrial fibrillation, catheter ablation, cryoballoon, cryotherapy

APPENDIX For an expanded Methods section and supplemental table and figures, please see the online version of this paper.