*Yeni Başlayan Atriyal Fibrilasyonda Ritm Tedavisi Hemen Yapılmalı mıdır?*

# EAST-AFNET 4, STOP-AF First, Cryo-FIRST, Early-AF

Dr. V. Kutay VURGUN
Ankara Liv Hospital

AFD atriyal fibrilasyon derneği
10. Atriyal Fibrilasyon Zirvesi 2021
11–13 Kasım 2021 • Calista Kongre Merkezi Antalya

- Çıkar çatışmam yoktur.

ESC European Society of Cardiology

European Heart Journal (2020) **42**, 373–498
doi:10.1093/eurheartj/ehaa612

**ESC GUIDELINES**

# 2020 AF

| | | |
|---|---|---|
| **AF catheter ablation after failure of drug therapy** | | |
| AF catheter ablation for PVI is recommended for rhythm control after one failed or intolerant class I or III AAD, to improve symptoms of AF recurrences in patients with[235–238,247,605–609,612,613,615–617,654,677,678,680,682,685,758,779,780,815]: | I | |
| • Paroxysmal AF, or | | A |
| • Persistent AF without major risk factors for AF recurrence, or | | A |
| • Persistent AF with major risk factors for AF recurrence. | | B |
| AF catheter ablation for PVI should be considered for rhythm control after one failed or intolerant to beta-blocker treatment to improve symptoms of AF recurrences in patients with paroxysmal and persistent AF.[246] | IIa | B |
| **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 | IIa | B |
| • Persistent AF without major risk factors for AF recurrence.[253–255,264,598–601,609,610,633,636,641,724,745,746,832] | IIb | C |
| 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, independent of their symptom status.[666,675,676] | I | B |
| • 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] | IIa | B |
| AF catheter ablation for PVI should be considered as a strategy to avoid pacemaker implantation in patients with AF-related bradycardia or symptomatic pre-automaticity pause after AF conversion considering the clinical situation.[816–818] | IIa | C |

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Early Rhythm-Control Therapy in Patients with Atrial Fibrillation

P. Kirchhof, A.J. Camm, A. Goette, A. Brandes, L. Eckardt, A. Elvan, T. Fetsch, I.C. van Gelder, D. Haase, L.M. Haegeli, F. Hamann, H. Heidbüchel, G. Hindricks, J. Kautzner, K.-H. Kuck, L. Mont, G.A. Ng, J. Rekosz, N. Schoen, U. Schotten, A. Suling, J. Taggeselle, S. Themistoclakis, E. Vettorazzi, P. Vardas, K. Wegscheider, S. Willems, H.J.G.M. Crijns, and G. Breithardt, for the EAST-AFNET 4 Trial Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 28, 2021 VOL. 384 NO. 4

## Cryoablation or Drug Therapy for Initial Treatment of Atrial Fibrillation

Jason G. Andrade, M.D., George A. Wells, Ph.D., Marc W. Deyell, M.D., Matthew Bennett, M.D., Vidal Essebag, M.D., Ph.D., Jean Champagne, M.D., Jean-Francois Roux, M.D., Derek Yung, M.D., Allan Skanes, M.D., Yaariv Khaykin, M.D., Carlos Morillo, M.D., Umjeet Jolly, M.D., Paul Novak, M.D., Evan Lockwood, M.D., Guy Amit, M.D., Paul Angaran, M.D., John Sapp, M.D., Stephan Wardell, M.D., Sandra Lauck, Ph.D., Laurent Macle, M.D., and Atul Verma, M.D., for the EARLY-AF Investigators*

ORIGINAL ARTICLE

# Cryoballoon Ablation as Initial Therapy for Atrial Fibrillation

Oussama M. Wazni, M.D., Gopi Dandamudi, M.D., Nitesh Sood, M.D., Robert Hoyt, M.D., Jaret Tyler, M.D., Sarfraz Durrani, M.D., Mark Niebauer, M.D., Kevin Makati, M.D., Blair Halperin, M.D., Andre Gauri, M.D., Gustavo Morales, M.D., Mingyuan Shao, Ph.D., Jeffrey Cerkvenik, M.S., Rachelle E. Kaplon, Ph.D., and Steven E. Nissen, M.D., for the STOP AF First Trial Investigators*

ESC European Society of Cardiology

Europace (2021) **00**, 1–9
doi:10.1093/europace/euab029

CLINICAL RESEARCH

## Cryoballoon ablation vs. antiarrhythmic drugs: first-line therapy for patients with paroxysmal atrial fibrillation

**Malte Kuniss [1]*, Nikola Pavlovic [2], Vedran Velagic[3], Jean Sylvain Hermida[4], Stewart Healey[5], Giuseppe Arena[6], Nicolas Badenco[7], Christian Meyer [8], Jian Chen[9], Saverio Iacopino[10], Frédéric Anselme [11], Douglas L. Packer[12], Heinz-Friedrich Pitschner[1], Carlo de Asmundis[13], Stephan Willems[14], Fabio Di Piazza[15], Daniel Becker[16], and Gian-Battista Chierchia[13]; for the Cryo-FIRST Investigators**

## BACKGROUND

Despite improvements in the management of atrial fibrillation, patients with this condition remain at increased risk for cardiovascular complications. It is unclear whether early rhythm-control therapy can reduce this risk.

## METHODS

In this international, investigator-initiated, parallel-group, open, blinded-outcome-assessment trial, we randomly assigned patients who had early atrial fibrillation (diagnosed ≤1 year before enrollment) and cardiovascular conditions to receive either early rhythm control or usual care. Early rhythm control included treatment with antiarrhythmic drugs or atrial fibrillation ablation after randomization. Usual care limited rhythm control to the management of atrial fibrillation–related symptoms. The first primary outcome was a composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome; the second primary outcome was the number of nights spent in the hospital per year. The primary safety outcome was a composite of death, stroke, or serious adverse events related to rhythm-control therapy. Secondary outcomes, including symptoms and left ventricular function, were also evaluated.

## RESULTS

In 135 centers, 2789 patients with early atrial fibrillation (median time since diagnosis, 36 days) underwent randomization. The trial was stopped for efficacy at the third interim analysis after a median of 5.1 years of follow-up per patient. A first-primary-outcome event occurred in 249 of the patients assigned to early rhythm control (3.9 per 100 person-years) and in 316 patients assigned to usual care (5.0 per 100 person-years) (hazard ratio, 0.79; 96% confidence interval, 0.66 to 0.94; P=0.005). The mean (±SD) number of nights spent in the hospital did not differ significantly between the groups (5.8±21.9 and 5.1±15.5 days per year, respectively; P=0.23). The percentage of patients with a primary safety outcome event did not differ significantly between the groups; serious adverse events related to rhythm-control therapy occurred in 4.9% of the patients assigned to early rhythm control and 1.4% of the patients assigned to usual care. Symptoms and left ventricular function at 2 years did not differ significantly between the groups.

## CONCLUSIONS

Early rhythm-control therapy was associated with a lower risk of cardiovascular outcomes than usual care among patients with early atrial fibrillation and cardiovascular conditions. (Funded by the German Ministry of Education and Research and others; EAST-AFNET 4 ISRCTN number, ISRCTN04708680; ClinicalTrials.gov number, NCT01288352; EudraCT number, 2010-021258-20.)

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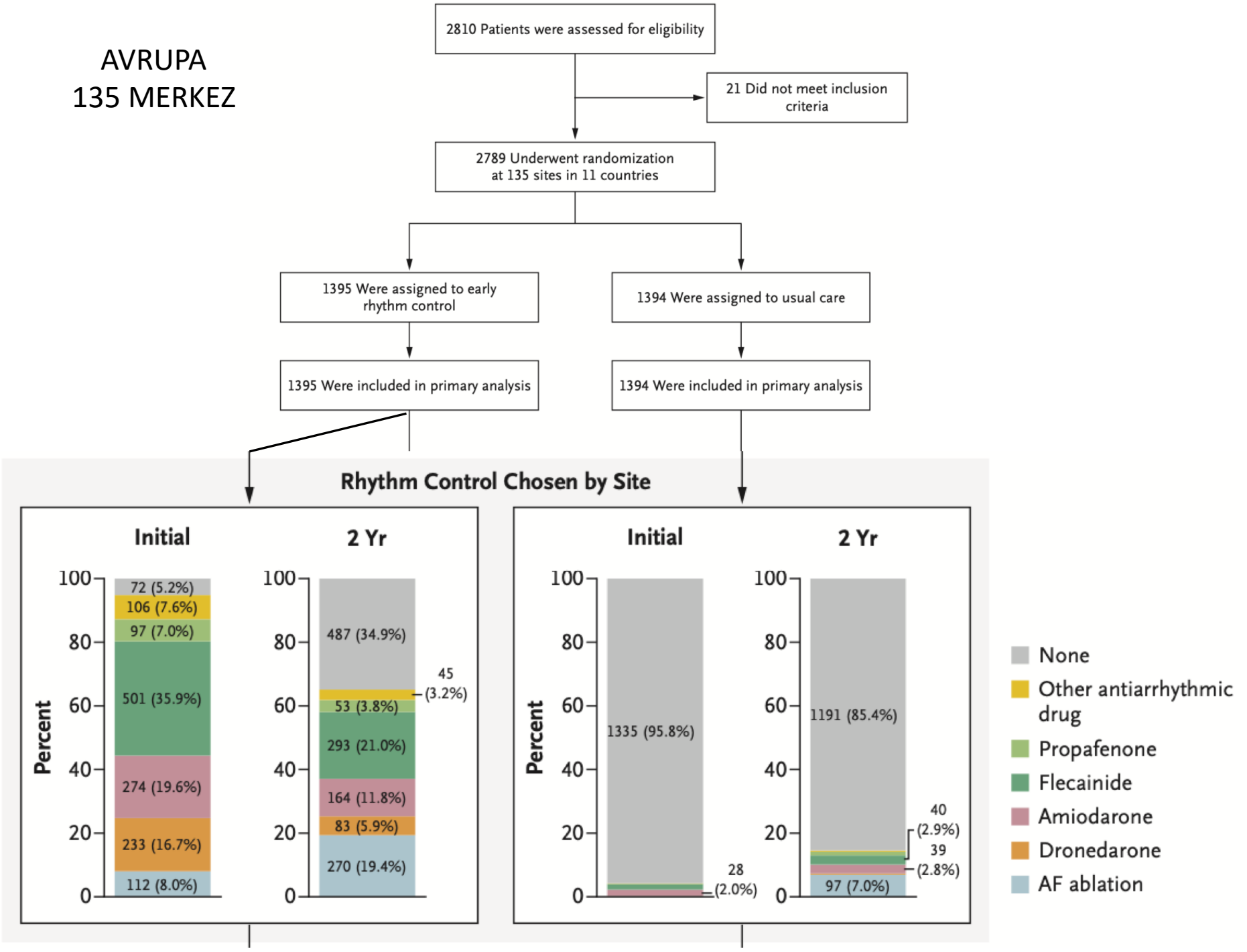
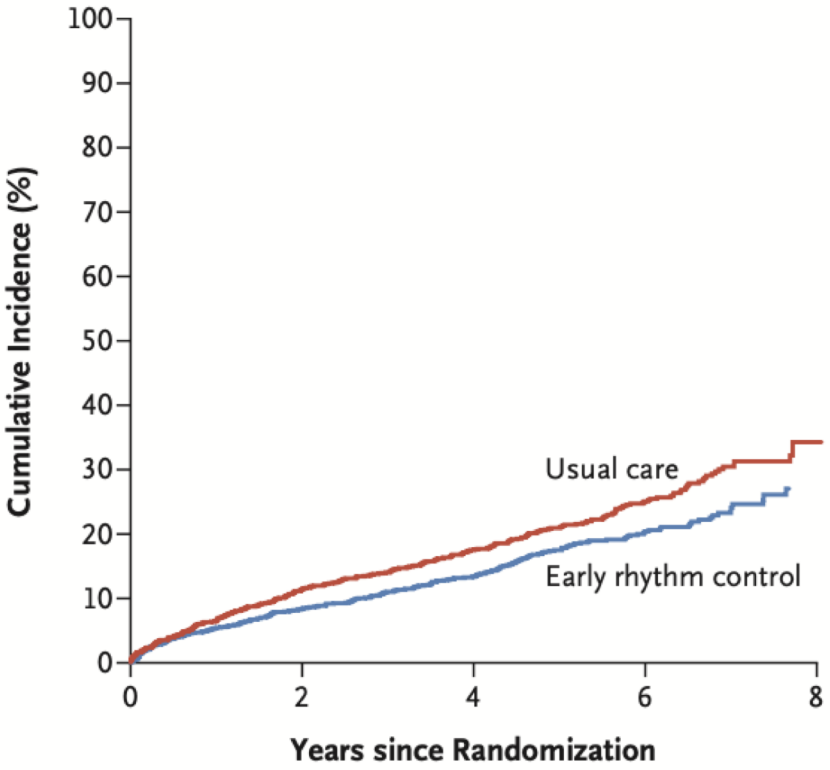


**Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.***

| Characteristic | Early Rhythm Control (N=1395) | Usual Care (N=1394) |
|---|---|---|
| Age — yr | 70.2±8.4 | 70.4±8.2 |
| Female sex — no. (%) | 645 (46.2) | 648 (46.5) |
| Body-mass index† | 29.2±5.4 | 29.3±5.4 |
| Type of atrial fibrillation — no./total no. (%) | | |
| First episode | 528/1391 (38.0) | 520/1394 (37.3) |
| Paroxysmal | 501/1391 (36.0) | 493/1394 (35.4) |
| Persistent | 362/1391 (26.0) | 381/1394 (27.3) |
| Sinus rhythm at baseline — no./total no. (%) | 762/1389 (54.9) | 743/1393 (53.3) |
| Median days since atrial fibrillation diagnosis (IQR)‡ | 36.0 (6.0–114.0) | 36.0 (6.0–112.0) |
| Absence of atrial fibrillation symptoms — no./total no. (%)§ | 395/1305 (30.3) | 406/1328 (30.6) |
| Previous cardioversion — no./total no. (%) | 546/1364 (40.0) | 543/1389 (39.1) |
| **Concomitant cardiovascular conditions** | | |
| Previous stroke or transient ischemic attack — no. (%) | 175 (12.5) | 153 (11.0) |
| At least mild cognitive impairment — no./total no. (%)¶ | 582/1326 (43.9) | 584/1341 (43.5) |
| Arterial hypertension — no. (%) | 1230 (88.2) | 1220 (87.5) |
| Blood pressure — mm Hg‖ | | |
| Systolic | 136.5±19.4 | 137.5±19.3 |
| Diastolic | 80.9±12.1 | 81.3±12.0 |
| Stable heart failure — no. (%)** | 396 (28.4) | 402 (28.8) |
| $CHA_2DS_2$-VASc score†† | 3.4±1.3 | 3.3±1.3 |
| Valvular heart disease — no./total no. (%) | 609/1389 (43.8) | 642/1391 (46.2) |
| Chronic kidney disease of MDRD stage 3 or 4 — no. (%)‡‡ | 172 (12.3) | 179 (12.8) |
| Medication at discharge — no./total no. (%)§§ | | |
| Oral anticoagulation with NOAC or VKA | 1267/1389 (91.2) | 1250/1393 (89.7) |
| Digoxin or digitoxin | 46/1389 (3.3) | 85/1393 (6.1) |
| Beta-blocker | 1058/1389 (76.2) | 1191/1393 (85.5) |
| ACE inhibitors or angiotensin II receptor blocker | 953/1389 (68.6) | 979/1393 (70.3) |
| Mineralocorticoid-receptor antagonist | 90/1389 (6.5) | 92/1393 (6.6) |
| Diuretic | 559/1389 (40.2) | 561/1393 (40.3) |
| Statin | 628/1389 (45.2) | 568/1393 (40.8) |
| Platelet inhibitor | 229/1389 (16.5) | 226/1393 (16.2) |

**Table 2. Efficacy Outcomes.***

| Outcome | Early Rhythm Control | Usual Care | Treatment Effect |
|---|---|---|---|
| First primary outcome — events/person-yr (incidence/100 person-yr) | 249/6399 (3.9) | 316/6332 (5.0) | 0.79 (0.66 to 0.94)† |
| Components of first primary outcome — events/person-yr (incidence/100 person-yr) | | | |
| Death from cardiovascular causes | 67/6915 (1.0) | 94/6988 (1.3) | 0.72 (0.52 to 0.98)‡ |
| Stroke | 40/6813 (0.6) | 62/6856 (0.9) | 0.65 (0.44 to 0.97)‡ |
| Hospitalization with worsening of heart failure | 139/6620 (2.1) | 169/6558 (2.6) | 0.81 (0.65 to 1.02)‡ |
| Hospitalization with acute coronary syndrome | 53/6762 (0.8) | 65/6816 (1.0) | 0.83 (0.58 to 1.19)‡ |
| Second primary outcome — nights spent in hospital/yr | 5.8±21.9 | 5.1±15.5 | 1.08 (0.92 to 1.28)§ |
| Key secondary outcomes at 2 yr | | | |
| Change in left ventricular ejection fraction — % | 1.5±9.8 | 0.8±9.8 | 0.23 (–0.46 to –0.91)¶ |
| Change in EQ-5D score‖ | –1.0±21.4 | –2.7±22.3 | 1.07 (–0.68 to 2.82)¶ |
| Change in SF-12 Mental Score** | 0.7±10.6 | 1.6±10.1 | –1.20 (–2.04 to –0.37)¶ |
| Change in SF-12 Physical Score** | 0.3±8.5 | 0.1±8.2 | 0.33 (–0.39 to 1.06)¶ |
| Change in MoCA score | 0.1±3.3 | 0.1±3.2 | –0.14 (–0.39 to 0.12)¶ |
| Sinus rhythm — no. of patients with feature/total no. (%) | 921/1122 (82.1) | 687/1135 (60.5) | 3.13 (2.55 to 3.84)†† |
| Asymptomatic — no. of patients with feature/total no. (%)‡‡ | 861/1159 (74.3) | 850/1171 (72.6) | 1.14 (0.93 to 1.40)†† |




**No. at Risk**

| | | | | | |
|---|---|---|---|---|---|
| Usual care | 1394 | 1169 | 888 | 405 | 34 |
| Early rhythm control | 1395 | 1193 | 913 | 404 | 26 |

**Figure 2. Aalen–Johansen Cumulative-Incidence Curves for the First Primary Outcome.**

The first primary outcome was a composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome.

**Table 3. Safety Outcomes.***

| Outcome | Early Rhythm Control (N=1395) | Usual Care (N=1394) |
|---|---|---|
| | *number (percent)* | |
| Primary composite safety outcome | 231 (16.6) | 223 (16.0) |
| Stroke | 40 (2.9) | 62 (4.4) |
| Death | 138 (9.9) | 164 (11.8) |
| Serious adverse event of special interest related to rhythm-control therapy | 68 (4.9) | 19 (1.4) |
| Serious adverse event related to antiarrhythmic drug therapy | | |
| Nonfatal cardiac arrest | 1 (0.1) | 1 (0.1) |
| Toxic effects of atrial fibrillation–related drug therapy | 10 (0.7) | 3 (0.2) |
| Drug-induced bradycardia | 14 (1.0) | 5 (0.4) |
| Atrioventricular block | 2 (0.1) | 0 |
| Torsades de pointes tachycardia | 1 (0.1) | 0 |
| Serious adverse event related to atrial fibrillation ablation | | |
| Pericardial tamponade | 3 (0.2) | 0 |
| Major bleeding related to atrial fibrillation ablation | 6 (0.4) | 0 |
| Nonmajor bleeding related to atrial fibrillation ablation | 1 (0.1) | 2 (0.1) |
| Other serious adverse event of special interest related to rhythm-control therapy | | |
| Blood pressure–related event† | 1 (0.1) | 0 |
| Hospitalization for atrial fibrillation | 11 (0.8) | 3 (0.2) |
| Other cardiovascular event | 5 (0.4) | 1 (0.1) |
| Other event | 1 (0.1) | 3 (0.2) |
| Syncope | 4 (0.3) | 1 (0.1) |
| Hospitalization for worsening of heart failure with decompensated heart failure | 3 (0.2) | 0 |
| Implantation of a pacemaker, defibrillator, cardiac resynchronization device, or any other cardiac device | 8 (0.6) | 4 (0.3) |

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**BACKGROUND**

In patients with symptomatic paroxysmal atrial fibrillation that has not responded to medication, catheter ablation is more effective than antiarrhythmic drug therapy for maintaining sinus rhythm. However, the safety and efficacy of cryoballoon ablation as initial first-line therapy have not been established.

**METHODS**

We performed a multicenter trial in which patients 18 to 80 years of age who had paroxysmal atrial fibrillation for which they had not previously received rhythm-control therapy were randomly assigned (1:1) to receive treatment with antiarrhythmic drugs (class I or III agents) or pulmonary vein isolation with a cryoballoon. Arrhythmia monitoring included 12-lead electrocardiography conducted at baseline and at 1, 3, 6, and 12 months; patient-activated telephone monitoring conducted weekly and when symptoms were present during months 3 through 12; and 24-hour ambulatory monitoring conducted at 6 and 12 months. The primary efficacy end point was treatment success (defined as freedom from initial failure of the procedure or atrial arrhythmia recurrence after a 90-day blanking period to allow recovery from the procedure or drug dose adjustment, evaluated in a Kaplan–Meier analysis). The primary safety end point was assessed in the ablation group only and was a composite of several procedure-related and cryoballoon system–related serious adverse events.

**RESULTS**

Of the 203 participants who underwent randomization and received treatment, 104 underwent ablation, and 99 initially received drug therapy. In the ablation group, initial success of the procedure was achieved in 97% of patients. The Kaplan–Meier estimate of the percentage of patients with treatment success at 12 months was 74.6% (95% confidence interval [CI], 65.0 to 82.0) in the ablation group and 45.0% (95% CI, 34.6 to 54.7) in the drug-therapy group ($P<0.001$ by log-rank test). Two primary safety end-point events occurred in the ablation group (Kaplan–Meier estimate of the percentage of patients with an event within 12 months, 1.9%; 95% CI, 0.5 to 7.5).

**CONCLUSIONS**

Cryoballoon ablation as initial therapy was superior to drug therapy for the prevention of atrial arrhythmia recurrence in patients with paroxysmal atrial fibrillation. Serious procedure-related adverse events were uncommon. (Supported by Medtronic; STOP AF First ClinicalTrials.gov number, NCT03118518.)

**Table 1. Characteristics of the Patients.***

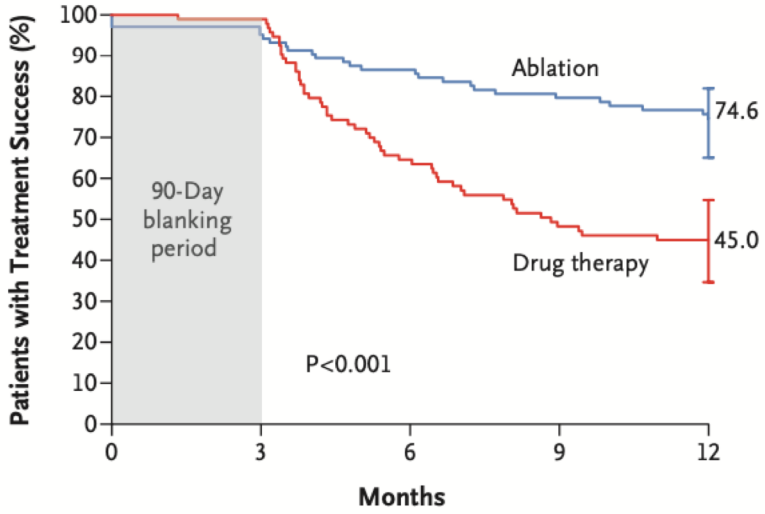
| Characteristic | Ablation (N=104) | Drug Therapy (N=99) |
|---|---|---|
| Age — yr | 60.4±11.2 | 61.6±11.2 |
| Male sex — no. (%) | 63 (61) | 57 (58) |
| Time since paroxysmal atrial fibrillation onset — yr | 1.3±2.5† | 1.3±2.3‡ |
| Left atrial diameter — mm | 38.7±5.7 | 38.2±5.4‡ |
| Left ventricular ejection fraction — % | 60.9±6.0 | 61.1±5.9‡ |
| Medical characteristics — no. (%) | | |
| Hypertension | 58 (56) | 57 (58) |
| Diabetes | 15 (14) | 17 (17) |
| Myocardial infarction | 4 (4) | 2 (2) |
| Coronary artery disease | 13 (12) | 12 (12) |
| Congestive heart failure | 1 (1) | 3 (3) |
| Stroke | 0 | 3 (3) |
| Transient ischemic attack | 2 (2) | 0 |
| Cardiac valve dysfunction | 8 (8) | 9 (9) |
| Chronic obstructive pulmonary disease | 5 (5) | 6 (6) |
| Sleep apnea | 26 (25) | 20 (20) |
| Renal dysfunction | 1 (1) | 2 (2) |
| $CHA_2DS_2$-VASc score — no. (%)§ | | |
| 0 | 20 (19) | 16 (16) |
| 1 | 28 (27) | 28 (28) |
| 2 | 33 (32) | 19 (19) |
| 3 | 12 (12) | 22 (22) |
| >3 | 11 (11) | 14 (14) |
| Baseline medications | | |
| Anticoagulant | 72 (69) | 68 (69) |
| Aspirin | 21 (20) | 13 (13) |
| Beta-blocker | 6 (6) | 9 (9) |
| Calcium-channel blocker | 10 (10) | 4 (4) |
| Cardioversions in the previous 12 mo | | |
| Electrical | 19 (18) | 15 (15) |
| Pharmacologic | 8 (8) | 14 (14) |
| Median time from randomization to initiation of treatment (IQR) — days | 24 (16–28) | 2 (0–8) |

**Table 2. Antiarrhythmic Drug Dosing in the Drug-Therapy Group.***

| Drug and Total Daily Dose | At End of Blanking Period (N=94) | At Treatment Failure, 12 Months, or Exit (N=94) |
|---|---|---|
| | *no. of patients (%)* | |
| Flecainide | | |
| 50 mg† | 2 (2) | 2 (2) |
| 100 mg | 22 (23) | 21 (22) |
| 150 mg | 0 | 1 (1) |
| 200 mg | 28 (30) | 27 (29) |
| 300 mg | 3 (3) | 2 (2) |
| 375 mg | 1 (1) | 1 (1) |
| As needed† | 2 (2) | 2 (2) |
| Propafenone | | |
| 450 mg | 6 (6) | 7 (7) |
| 650 mg | 1 (1) | 1 (1) |
| Dronedarone E-4031 | | |
| 800 mg | 11 (12) | 10 (11) |
| Sotalol | | |
| 80 mg | 1 (1) | 1 (1) |
| 160 mg | 6 (6) | 6 (6) |
| Amiodarone | | |
| 200 mg | 1 (1) | 0 |
| 400 mg | 1 (1) | 1 (1) |
| Not taking a class I or III antiarrhythmic drug | 9 (10) | 12 (13) |

**Table 3. Primary Efficacy End-Point Events within 12 Months.***

| Event | Ablation (N=104) | Drug Therapy (N=99) |
|---|---|---|
| | *no. of patients* | |
| Primary efficacy end-point event | 26 | 51 |
| Initial failure of the procedure | 3 | — |
| Left atrial nonpulmonary vein isolation ablation | 1† | — |
| Inability to isolate all accessible targeted pulmonary veins | 2 | — |
| Use of a nontrial device in the left atrium | 1† | — |
| Documented atrial fibrillation, atrial tachycardia, or atrial flutter after 90 days | 21 | 35 |
| Ablation in left atrium‡ | 0 | 15 |
| Cardioversion after 90 days | 0 | 1 |
| Class I or III antiarrhythmic drug use after 90 days | 2 | — |




**No. at Risk**

| | | | | | |
|---|---|---|---|---|---|
| Ablation | 104 | 99 | 88 | 81 | 70 |
| Drug therapy | 99 | 93 | 60 | 44 | 39 |

**Aims**

Treatment guidelines for patients with atrial fibrillation (AF) suggest that patients should be managed with an anti-arrhythmic drug (AAD) before undergoing catheter ablation (CA). This study evaluated whether pulmonary vein isolation employing cryoballoon CA is superior to AAD therapy for the prevention of atrial arrhythmia (AA) recurrence in rhythm control naive patients with paroxysmal AF (PAF).

**Methods and results**

A total of 218 treatment naive patients with symptomatic PAF were randomized (1 : 1) to cryoballoon CA (Arctic Front Advance, Medtronic) or AAD (Class I or III) and followed for 12 months. The primary endpoint was ≥1 episode of recurrent AA (AF, atrial flutter, or atrial tachycardia) >30 s after a prespecified 90-day blanking period. Secondary endpoints included the rate of serious adverse events (SAEs) and recurrence of symptomatic palpitations (evaluated via patient diaries). Freedom from AA was achieved in 82.2% of subjects in the cryoballoon arm and 67.6% of subjects in the AAD arm (HR = 0.48, $P = 0.01$). There were no group differences in the time-to-first (HR = 0.76, $P = 0.28$) or overall incidence [incidence rate ratio (IRR)=0.79, $P = 0.28$] of SAEs. The incidence rate of symptomatic palpitations was lower in the cryoballoon (7.61 days/year) compared with the AAD arm (18.96 days/year; IRR = 0.40, $P < 0.001$).

**Conclusions**

Cryoballoon CA was superior to AAD therapy, significantly reducing AA recurrence in treatment naive patients with PAF. Additionally, cryoballoon CA was associated with lower symptom recurrence and a similar rate of SAEs compared with AAD therapy.

AVUSTRALYA, AVRUPA, LATİN AMERİKA
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**Table 1** **Baseline subject characteristics**

| | Cryoballoon CA ($n = 107$) | AAD ($n = 111$) |
|---|---|---|
| Demographics and echocardiographic characteristics | | |
| Age (years) | 50.5 (13.1) | 54.1 (13.4) |
| Sex, male | 76 (71.0%) | 72 (64.9%) |
| Time from first ECG-documented AF to enrolment (years) | 0.7 (1.5) | 0.8 (2.1) |
| Left atrial diameter (short axis) (mm) | 37.0 (5.9) | 38.0 (4.9) |
| Left atrial diameter (long axis) (mm) | 46.8 (8.2) | 47.7 (6.3) |
| Left ventricular ejection fraction (%) | 62.8 (5.4) | 63.7 (5.4) |
| EHRA class | | |
| Class I | 0 (0.0%) | 0 (0.0%) |
| Class II | 75 (70.1%) | 83 (74.8%) |
| Class III | 30 (28.0%) | 25 (22.5%) |
| Class IV | 2 (1.9%) | 1 (0.9%) |
| Medical history | | |
| Hypertension | 33 (30.8%) | 40 (36.0%) |
| Diabetes | 1 (0.9%) | 4 (3.6%) |
| Hyperlipidaemia | 23 (21.5%) | 25 (22.5%) |
| Myocardial infarction | 2 (1.9%) | 0 (0.0%) |
| Coronary artery disease | 2 (1.9%) | 1 (0.9%) |
| Congestive heart failure | 0 (0.0%) | 0 (0.0%) |
| Stroke | 0 (0.0%) | 0 (0.0%) |
| Transient ischaemic attack | 0 (0.0%) | 1 (0.9%) |
| Valve dysfunction | 3 (2.8%) | 2 (1.8%) |
| $CHA_2DS_2$-VASc score | | |
| 0 | 49 (45.8%) | 38 (34.2%) |
| 1 | 33 (30.8%) | 40 (36.1%) |
| 2 | 13 (12.2%) | 15 (13.5%) |
| 3 | 4 (3.7%) | 10 (9.0%) |
| 4 | 3 (2.8%) | 2 (1.8%) |
| Baseline medications | | |
| Anticoagulant | 38 (35.5%) | 49 (44.1%) |
| Acetylsalicylic acid | 5 (4.7%) | 7 (6.3%) |
| β-Blocker | 54 (50.5%) | 56 (50.5%) |
| Calcium channel blocker | 9 (8.4%) | 15 (13.5%) |

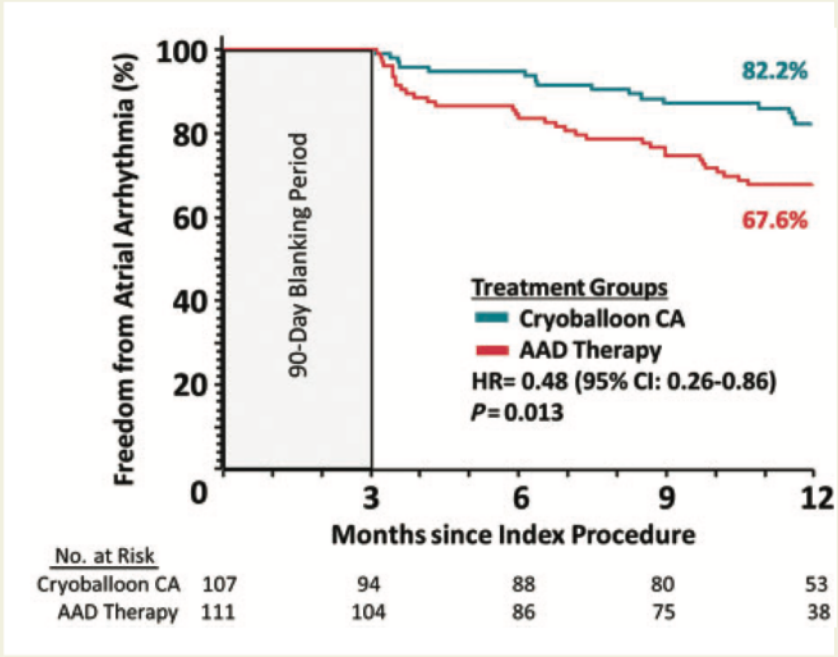



**Figure 2** Time to first atrial arrhythmia recurrence in the intention-to-treat cohort.

**Table 3** **Reason for primary endpoint failure through 12 months**

| Primary endpoint failure event | Cryoballoon CA | AAD |
|---|---|---|
| Total | 16 | 33 |
| Atrial arrhythmia recurrence | 15 | 33 |
| Atrial fibrillation | 12 | 23 |
| Atrial flutter | 0 | 1 |
| Atrial tachycardia | 3 | 7 |
| Atrial fibrillation, atrial flutter | 0 | 1 |
| Atrial fibrillation, atrial flutter, and atrial tachycardia | 0 | 1 |
| Reablation | 1 | 0 |
| Cardioversion | 0 | 0 |

AAD, antiarrhythmic drug; CA, catheter ablation.

**Table 2** **Antiarrhythmic drug therapy and dosing**

| Drug | Daily dose (mg) | Therapy start ($n = 101$)a | Month 3 ($n = 97$)b | Month 12 ($n = 94$)c |
|---|---|---|---|---|
| Flecainide | 50 | 3 (2.9%) | 2 (2.1%) | 2 (2.1%) |
| | 80 | 1 (1.0%) | 0 (0%) | 0 (0%) |
| | 100 | 23 (22.3%) | 12 (12.4%) | 10 (10.6%) |
| | 120 | 0 (0%) | 1 (1.0%) | 0 (0%) |
| | 150 | 10 (9.7%) | 15 (15.5%) | 11 (11.7%) |
| | 200 | 24 (23.3%) | 13 (13.4%) | 12 (12.8%) |
| Propafenone | 300 | 14 (13.6%) | 9 (9.3%) | 9 (9.6%) |
| | 375 | 0 (0%) | 0 (0%) | 1 (1.1%) |
| | 450 | 13 (12.6%) | 13 (13.4%) | 10 (10.6%) |
| | 600 | 6 (5.8%) | 6 (6.2%) | 6 (6.4%) |
| Sotalol | 40 | 0 (0%) | 1 (1.0%) | 0 (0%) |
| | 80 | 3 (2.9%) | 7 (7.2%) | 4 (4.3%) |
| | 160 | 1 (1.0%) | 4 (4.1%) | 2 (2.1%) |
| | 240 | 1 (1.0%) | 0 (0%) | 0 (0%) |
| Dronedarone | 800 | 2 (1.9%) | 5 (5.2%) | 4 (4.3%) |
| Amiodarone | 200 | 0 (0%) | 2 (2.1%) | 1 (1.1%) |
| | 400 | 0 (0%) | 1 (1.0%) | 0 (0%) |
| Stopped AAD therapy[d] | NA | 0 (0%) | 6 (6.2%) | 22 (23.4%) |

**Table 4** Serious adverse events

| Adverse event, events (subjects) | Cryoballoon CA ($n$ = 107) | | | AAD ($n$ = 111) | | |
|---|---|---|---|---|---|---|
| | All | Procedure related | System related | All | Drug related | Procedure related (cross over) |
| Total | 42 (26) | 11 (9) | 2 (1) | 56 (37) | 4 (4) | 1 (1) |
| Acute coronary syndrome | 0 | 0 | 0 | 1 (1) | 0 | 0 |
| Acute kidney injury | 0 | 0 | 0 | 1 (1) | 0 | 0 |
| Adverse drug reaction | 0 | 0 | 0 | 3 (3) | 2 (2) | 0 |
| Arteriospasm coronary | 1 (1) | 1 (1) | 0 | 0 | 0 | 0 |
| Atrial arrhythmia recurrence | 15 (11) | 1 (1) | 0 | 34 (28) | 2 (2) | 0 |
| AVNRT | 1 (1) | 0 | 0 | 0 | 0 | 0 |
| Bronchitis | 1 (1) | 0 | 0 | 0 | 0 | 0 |
| Chest pain | 1 (1) | 0 | 0 | 0 | 0 | 0 |
| Gastrointestinal pain | 1 (1) | 0 | 0 | 0 | 0 | 0 |
| Impaired gastric emptying | 1 (1) | 1 (1) | 0 | 1 (1) | 0 | 0 |
| Impaired healing | 0 | 0 | 0 | 1 (1) | 0 | 0 |
| Lung disorder/infection | 4 (1) | 1 (1) | 0 | 0 | 0 | 0 |
| Non-sustained ventricular tachycardia | 0 | 0 | 0 | 1 (1) | 0 | 0 |
| Oedema peripheral | 0 | 0 | 0 | 1 (1) | 0 | 0 |
| Orthostatic hypotension | 0 | 0 | 0 | 1 (1) | 0 | 0 |
| Palpitations | 0 | 0 | 0 | 1 (1) | 0 | 0 |
| Pericardial disorder[a] | 3 (3) | 3 (3) | 1 (1) | 0 | 0 | 0 |
| Phrenic nerve paralysis | 0 | 0 | 0 0 | 1 (1)[b] | 0 | 1 (1) |
| Pneumonia | 1 (1) | 0 | 0 | 0 | 0 | 0 |
| Procedural failure[c] | 1 (1) | 1 (1) | 0 | 0 | 0 | 0 |
| Pyrexia | 1 (1) | 1.(1) | 0 | 0 | 0 | 0 |
| Syncope | 0 | 0 | 0 | 1 (1) | 0 | 0 |
| Transient ischaemic attack | 1 (1) | 1 (1) | 1 (1) | 0 | 0 | 0 |
| Vascular access site haemorrhage | 1 (1) | 1 (1) | 0 | 0 | 0 | 0 |
| Other | 9 (9) | 0 | 0 | 9 (7) | 0 | 0 |

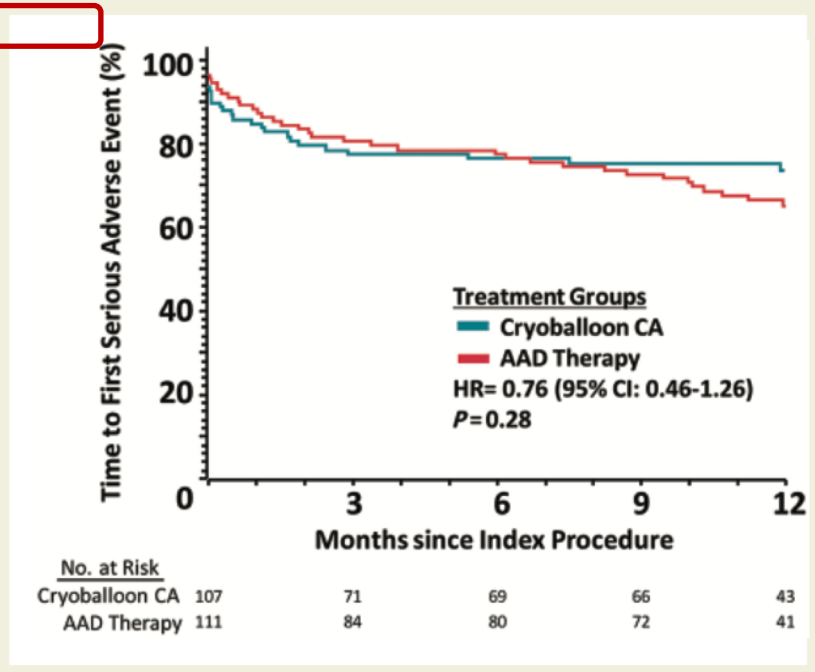



**Figure 3** Time to first serious adverse event in the intention-to-treat cohort.

KANADA
18MERKEZ


**BACKGROUND**

Guidelines recommend a trial of one or more antiarrhythmic drugs before catheter ablation is considered in patients with atrial fibrillation. However, first-line ablation may be more effective in maintaining sinus rhythm.

**METHODS**

We randomly assigned 303 patients with symptomatic, paroxysmal, untreated atrial fibrillation to undergo catheter ablation with a cryothermy balloon or to receive antiarrhythmic drug therapy for initial rhythm control. All the patients received an implantable cardiac monitoring device to detect atrial tachyarrhythmia. The follow-up period was 12 months. The primary end point was the first documented recurrence of any atrial tachyarrhythmia (atrial fibrillation, atrial flutter, or atrial tachycardia) between 91 and 365 days after catheter ablation or the initiation of an antiarrhythmic drug. The secondary end points included freedom from symptomatic arrhythmia, the atrial fibrillation burden, and quality of life.

**RESULTS**

At 1 year, a recurrence of atrial tachyarrhythmia had occurred in 66 of 154 patients (42.9%) assigned to undergo ablation and in 101 of 149 patients (67.8%) assigned to receive antiarrhythmic drugs (hazard ratio, 0.48; 95% confidence interval [CI], 0.35 to 0.66; P<0.001). Symptomatic atrial tachyarrhythmia had recurred in 11.0% of the patients who underwent ablation and in 26.2% of those who received antiarrhythmic drugs (hazard ratio, 0.39; 95% CI, 0.22 to 0.68). The median percentage of time in atrial fibrillation was 0% (interquartile range, 0 to 0.08) with ablation and 0.13% (interquartile range, 0 to 1.60) with antiarrhythmic drugs. Serious adverse events occurred in 5 patients (3.2%) who underwent ablation and in 6 patients (4.0%) who received antiarrhythmic drugs.

**CONCLUSIONS**

Among patients receiving initial treatment for symptomatic, paroxysmal atrial fibrillation, there was a significantly lower rate of atrial fibrillation recurrence with catheter cryoballoon ablation than with antiarrhythmic drug therapy, as assessed by continuous cardiac rhythm monitoring. (Funded by the Cardiac Arrhythmia Network of Canada and others; EARLY-AF ClinicalTrials.gov number, NCT02825979.)

**Table 1. Characteristics of the Patients at Baseline.***

| Characteristic | Ablation Group (N=154) | Antiarrhythmic Drug Group (N=149) |
|---|---|---|
| Age — yr | 57.7±12.3 | 59.5±10.6 |
| Male sex — no. (%) | 112 (72.7) | 102 (68.5) |
| BMI† | 30.9±14.2 | 29.7±9.3 |
| Obesity — no. (%)‡ | 56 (36.4) | 53 (35.6) |
| Tobacco use | 8 (5.2) | 10 (6.7) |
| Blood pressure — mm Hg | | |
| Systolic | 129.1±18.1 | 129.3±15.7 |
| Diastolic | 78.4±10.6 | 78.0±9.8 |
| Median yr since diagnosis of atrial fibrillation (IQR) | 1 (0–3) | 1 (0–4) |
| Paroxysmal atrial fibrillation — no. (%) | 147 (95.5) | 140 (94.0) |
| Symptomatic atrial fibrillation episodes/mo — median (IQR) | 3 (1–10) | 3 (1–10) |
| Previous cardioversion — no. (%) | 56 (36.4) | 63 (42.3) |
| Quality-of-life scores | | |
| AFEQT score§ | 61.4±19.7 | 57.4±20.6 |
| EQ-5D score¶ | 0.77±0.26 | 0.75±0.26 |
| EQ-VAS score‖ | 75.4±14.5 | 74.4±16.5 |
| CCS-SAF score of 3 or 4 — no. (%)** | 84 (54.5) | 84 (56.4) |
| $CHA_2DS_2$-VASc score†† | 1.9±1.0 | 1.9±1.1 |
| Medications — no. (%) | | |
| Beta-blocker | 85 (55.2) | 92 (61.7) |
| Nondihydropyridine calcium-channel blocker | 11 (7.1) | 10 (6.7) |
| ACE inhibitor | 24 (15.6) | 21 (14.1) |
| Angiotensin II receptor blocker | 20 (13.0) | 18 (12.1) |
| HMG-CoA reductase inhibitor | 38 (24.7) | 39 (26.2) |
| Mineralocorticoid-receptor antagonist | 1 (0.6) | 1 (0.7) |
| Previous use of class I or class III antiarrhythmic drug — no. (%)‡‡ | 40 (26.0) | 44 (29.5) |
| Oral anticoagulation — no. (%) | | |
| Warfarin | 5 (3.2) | 9 (6.0) |
| Non–vitamin K antagonist oral anticoagulant | 98 (63.6) | 87 (58.4) |
| Concomitant cardiovascular conditions — no. (%) | | |
| Hypertension | 57 (37.0) | 55 (36.9) |
| Ischemic heart disease | 12 (7.8) | 7 (4.7) |
| Sleep apnea | 32 (20.8) | 32 (21.5) |
| Previous stroke or transient ischemic attack | 4 (2.6) | 5 (3.4) |
| Stable heart failure§§ | 14 (9.1) | 14 (9.4) |
| Left atrial diameter — mm | 39.5±5.0 | 38.1±6.5 |
| Left atrial volume — $ml/m^2$ | 35.6±15.2 | 35.4±12.5 |
| Left ventricular ejection fraction — % | 59.6±7.0 | 59.8±7.6 |

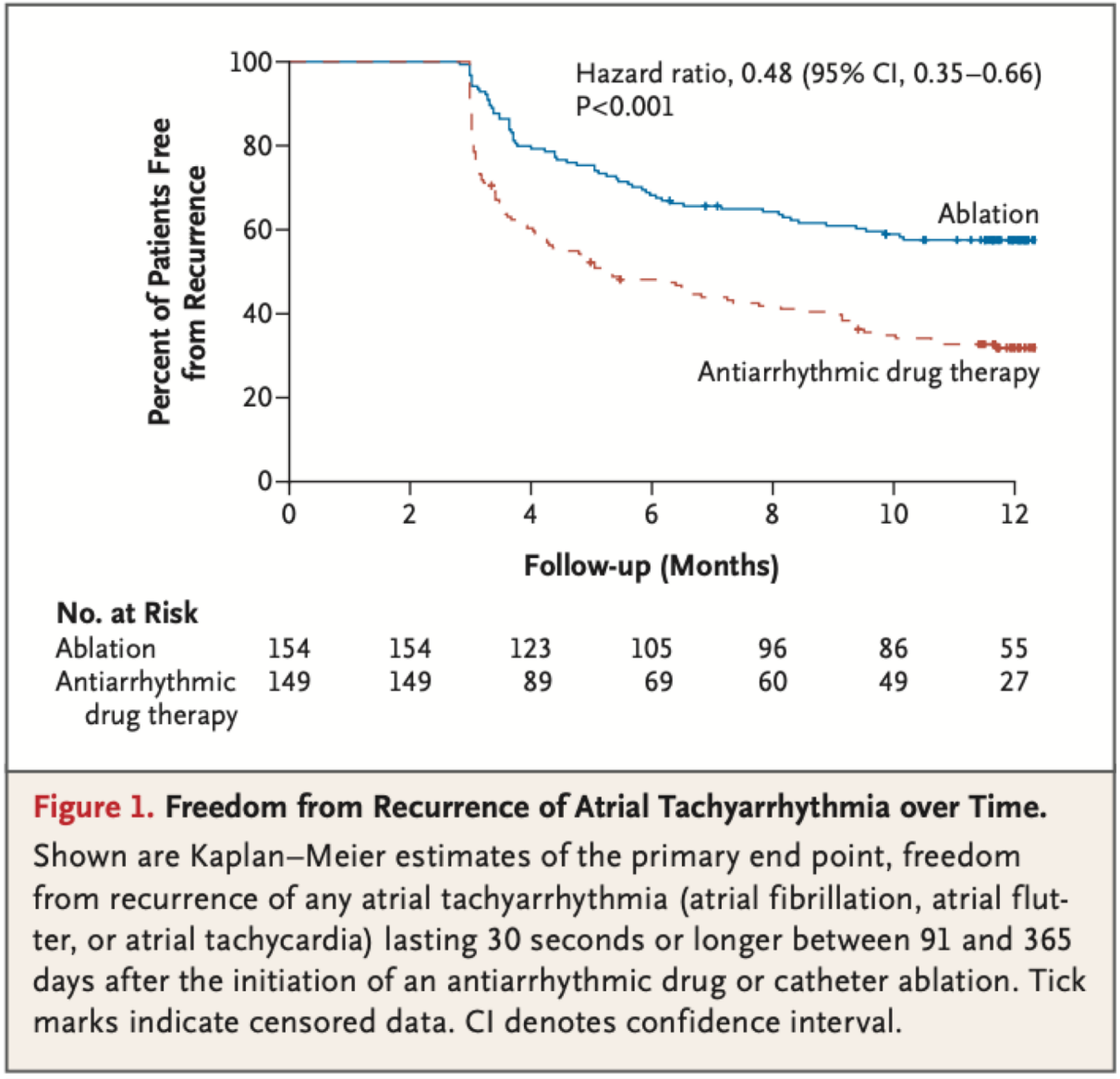



**Figure 1. Freedom from Recurrence of Atrial Tachyarrhythmia over Time.**

Shown are Kaplan–Meier estimates of the primary end point, freedom from recurrence of any atrial tachyarrhythmia (atrial fibrillation, atrial flutter, or atrial tachycardia) lasting 30 seconds or longer between 91 and 365 days after the initiation of an antiarrhythmic drug or catheter ablation. Tick marks indicate censored data. CI denotes confidence interval.

# Cryoballoon Ablation as Initial Treatment for Atrial Fibrillation

## *JACC* State-of-the-Art Review

Jason G. Andrade, MD,[a,b,c] Oussama M. Wazni, MD,[d] Malte Kuniss, MD,[e] Nathaniel M. Hawkins, MD,[a,b] Marc W. Deyell, MD, MSc,[a,b] Gian-Battista Chierchia, MD,[f] Steven Nissen, MD,[d] Atul Verma, MD,[g] George A. Wells, PhD,[h] Ricky D. Turgeon, PharmD[a]

JACC JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

**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)<br>• Symptoms<br>• Health care use<br>• Adverse events | • Quality of life (AFEQT, EQ5D)<br>• Symptoms<br>• Health care use<br>• Adverse events | • Quality of life (AFEQT)<br>• Health care use<br>• 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.

**TABLE 3** Rhythm Monitoring Protocols and Arrhythmia Detection

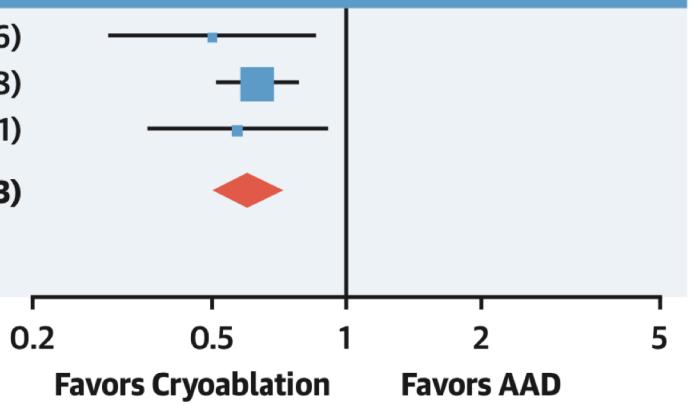
| | Cryo-FIRST | EARLY-AF | STOP-AF First |
|---|---|---|---|
| Primary outcome | Any recurrence of atrial tachyarrhythmia (AF, AT, AFL) lasting longer than 30 seconds | Any recurrence of atrial tachyarrhythmia (AF, AT, AFL) lasting longer than 30 seconds | Any recurrence of atrial tachyarrhythmia (AF, 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)<br>Weekly patient-activated transtelephonic event recorder (81% adherence) |
| Freedom from documented atrial tachyarrhythmia | 82.2% ablation<br>67.6% AAD | 57.1% ablation<br>32.2% AAD | 79.8% ablation<br>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) |

**FIGURE 2** Atrial Tachyarrhythmia Recurrence

## A Any Atrial Tachyarrhythmia

| Study | Cryoablation Events | Cryoablation Total | AAD Events | AAD Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Cryo-FIRST | 16 | 107 | 33 | 111 | 11.6% | 0.50 (0.29-0.86) |
| EARLY-AF | 66 | 154 | 101 | 149 | 73.0% | 0.63 (0.51-0.78) |
| STOP-AF First | 21 | 104 | 35 | 99 | 15.3% | 0.57 (0.36-0.91) |
| **Total (95% CI)** | | **365** | | **359** | **100.0%** | **0.61 (0.51-0.73)** |
| Total events | 103 | | 169 | | | |

Heterogeneity: Tau$^2$ = 0.00; chi-square = 0.72, df = 2 ($P$ = 0.70); $I^2$ = 0%
Test for overall effect: Z = 5.38 ($P$ < 0.00001)




## B Symptomatic Atrial Tachyarrhythmia

| Study | Cryoablation Events | Cryoablation Total | AAD Events | AAD Total | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| EARLY-AF | 17 | 154 | 39 | 149 | 0.42 (0.25-0.71) |

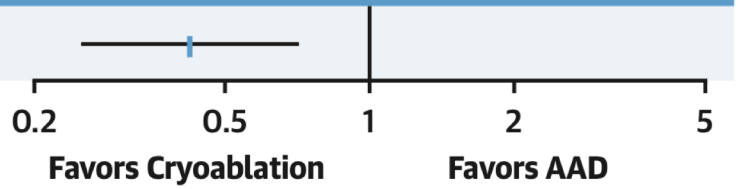
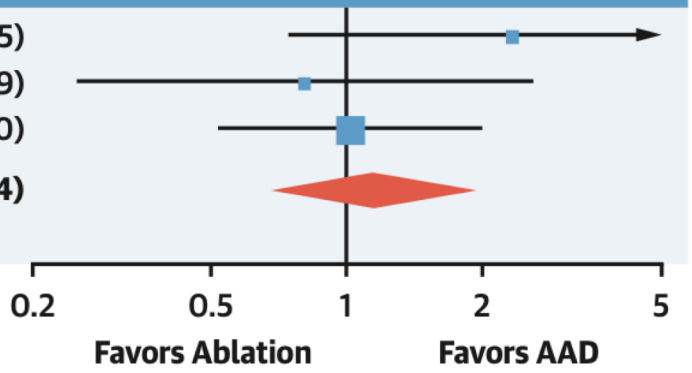


**FIGURE 5** Safety Outcomes

## 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)

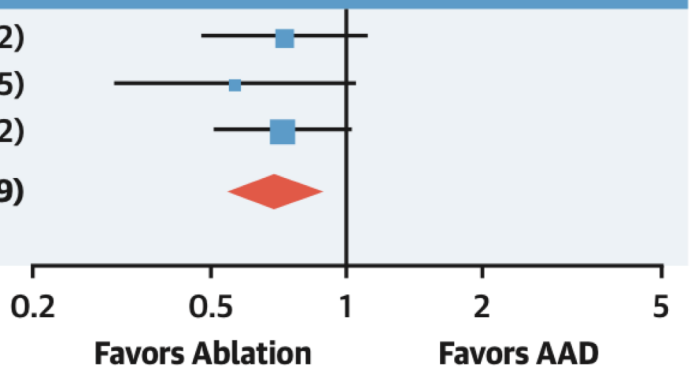
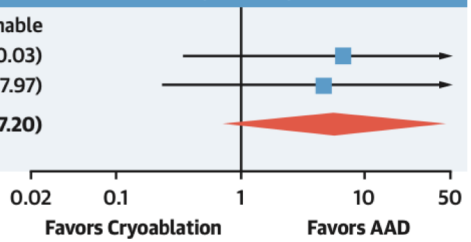


**FIGURE 6** Serious Adverse Events

## 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 | | | |

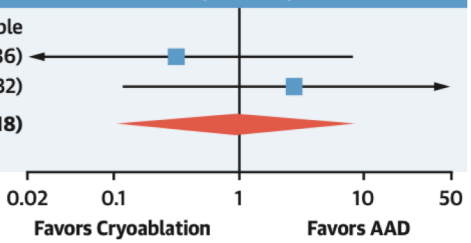
Heterogeneity: Tau$^2$ = 0.00; chi-square = 0.03, df = 1 ($P$ = 0.87); $I^2$ = 0%
Test for overall effect: Z = 1.61 ($P$ = 0.11)




## 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 | | | |

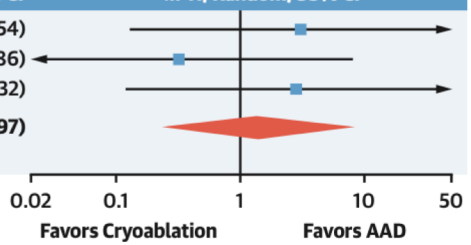
Heterogeneity: Tau$^2$ = 0.00; chi-square = 0.90, df = 1 ($P$ = 0.34); $I^2$ = 0%
Test for overall effect: Z = 0.03 ($P$ = 0.97)




## 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)

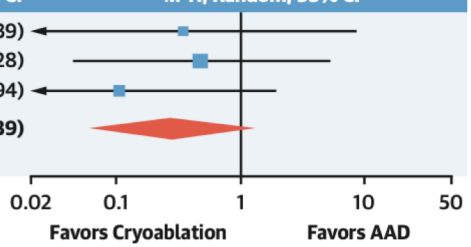
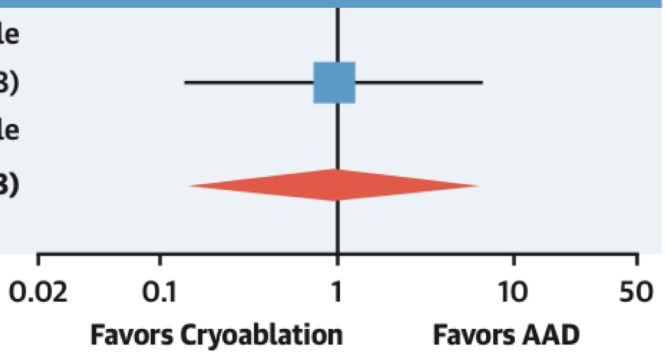


**FIGURE 6** Continued

## 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 | | | |

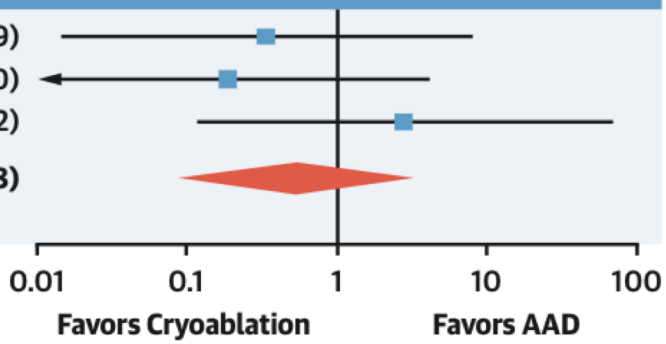
Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (*P* = 0.97)




## 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)



Europace
doi:10.1093/europace/euu376

CLINICAL RESEARCH

# Radiofrequency ablation vs. antiarrhythmic drug therapy as first line treatment of symptomatic atrial fibrillation: systematic review and meta-analysis

**Antti Hakalahti[1]*, Fausto Biancari[2], Jens Cosedis Nielsen[3], and M.J. Pekka Raatikainen[4,5]**

**Table 1** Characteristics of randomized trials comparing first-line radiofrequency ablation vs. antiarrhythmic drugs for atrial fibrillation

| Study | First author | Year | Study period | Type of study | No. of randomized patients (RFA/drugs) | No. lost to follow-up (RFA/drugs) | No. of patients included in the in primary analysis (RFA/drugs) | Inclusion criteria | Exclusion criteria |
|---|---|---|---|---|---|---|---|---|---|
| RAAFT-1 | Wazni | 2005 | 2001–2002 | Prospective, randomized, multicentre | 33/37 | 1/2 | 32/35 | Symptomatic AF for at least 3 months not treated by AADs | Age <18 years or >75 years, previous AF ablation, previous cardiac surgery, previous treatment with AADs, contraindication to OAC treatment |
| MANTRA-PAF | Cosedis-Nielsen | 2012 | 2005–2009 | Prospective, randomized, multicentre | 146/148 | 0/0 | 146/148 | Symptomatic PAF for at least 6 months. No episodes >7 days. No previous or ongoing treatment with class IC or III AADs | Age >70 years, previous or ongoing class IC or class III AADs, contraindication to class IC or class III AADs, previous ablation, LA diameter >5.0 cm, LVEF <40%, contraindication to OAC, moderate-to-severe mitral valve disease, NYHA III-IV, expected surgery for structural heart disease, secondary atrial fibrillation |
| RAAFT-2 | Morillo | 2014 | 2006–2010 | Prospective, randomized, multicentre | 66/61 | 0/0 | 66/61 | Symptomatic PAF for at least 6 months not treated by AADs | Age <18 years or >75 years, previous treatment with AADs, LVEF <40%, LA diameter >5.5 cm, left ventricular wall thickness >1.5 cm, valve disease, coronary artery disease, previous cardiac surgery within 6 months, previous AF ablation |

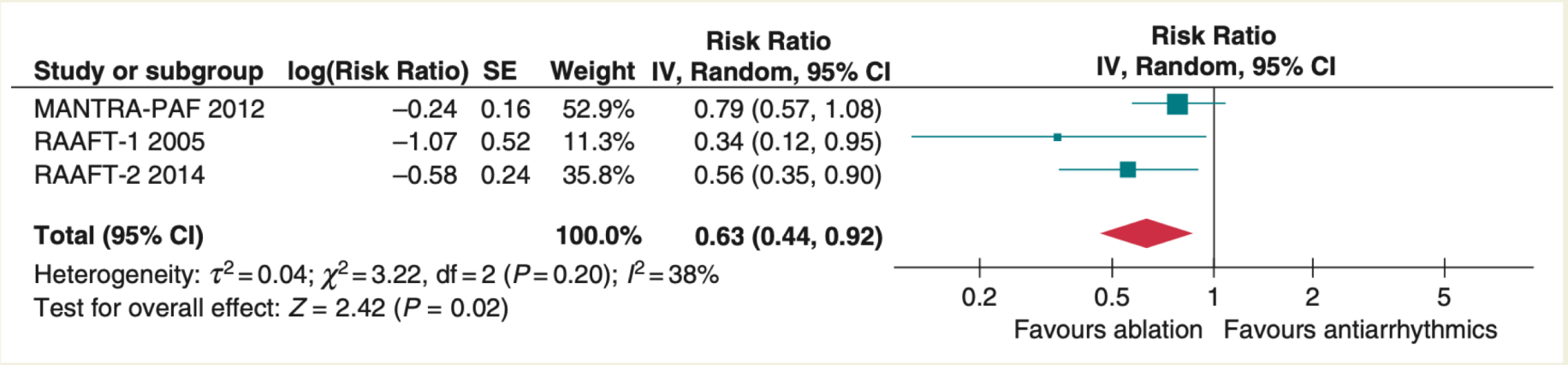



**Figure 2** Forest plot showing the risk of recurrence of atrial fibrillation after radiofrequency ablation or antiarrhythmic drug treatment in three randomized studies. RAAFT-2 study included also the occurrence of atrial tachycardia and flutter.

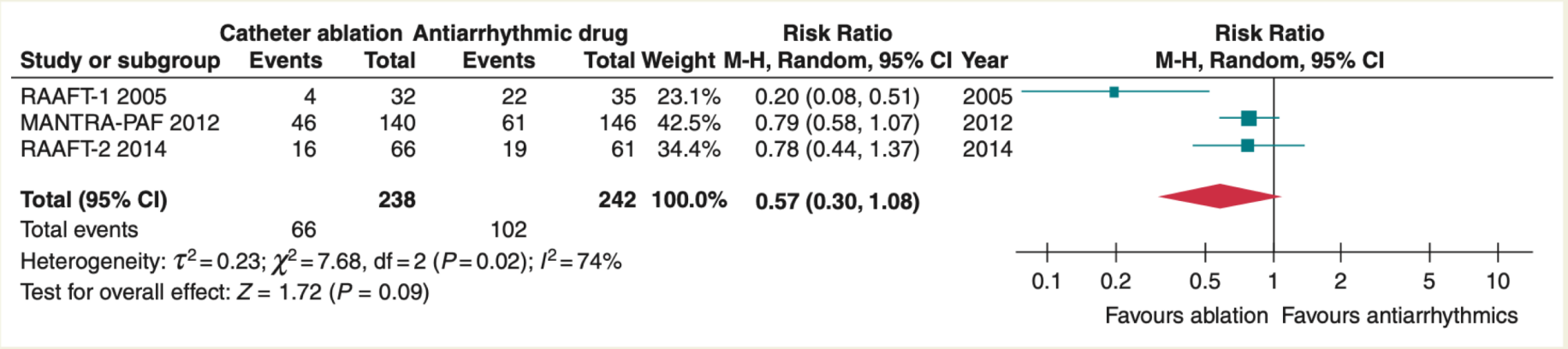



**Figure 3** Forest plot showing the risk of symptomatic atrial fibrillation after radiofrequency ablation or antiarrhythmic drug treatment in three randomized studies.

ESC European Society of Cardiology

European Heart Journal (2020) **42**, 373–498
doi:10.1093/eurheartj/ehaa612

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# 2020 AF

| | | |
|---|---|---|
| **AF catheter ablation after failure of drug therapy** | | |
| AF catheter ablation for PVI is recommended for rhythm control after one failed or intolerant class I or III AAD, to improve symptoms of AF recurrences in patients with[235–238,247,605–609,612,613,615–617,654,677,678,680,682,685,758,779,780,815]: | I | |
| • Paroxysmal AF, or | | A |
| • Persistent AF without major risk factors for AF recurrence, or | | A |
| • Persistent AF with major risk factors for AF recurrence. | | B |
| AF catheter ablation for PVI should be considered for rhythm control after one failed or intolerant to beta-blocker treatment to improve symptoms of AF recurrences in patients with paroxysmal and persistent AF.[246] | IIa | B |
| **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 ***STOP-AF First, Cryo-FIRST, Early-AF (?)*** | I (?!) | B |
| • Persistent AF without major risk factors for AF recurrence.[253–255,264,598–601,609,610,633,636,641,724,745,746,832] | IIb | C |
| 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, independent of their symptom status.[666,675,676] | I | B |
| • 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] | IIa | B |
| AF catheter ablation for PVI should be considered as a strategy to avoid pacemaker implantation in patients with AF-related bradycardia or symptomatic pre-automaticity pause after AF conversion considering the clinical situation.[816–818] | IIa | C |

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