Initial rhythm control with cryoballoon ablation vs drug therapy: Impact on quality of life and symptoms

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Background Cryoballoon ablation (CBA) as a first-line rhythm control strategy is superior to antiarrhythmic drugs (AADs) for preventing atrial fibrillation (AF) recurrence; the impact of first-line CBA on quality of life (QoL) and symptoms has not been well characterized.

Methods Patients aged 18 to 75 with symptomatic paroxysmal AF naïve to rhythm control therapy were randomized (1:1) to CBA (Arctic Front Advance, Medtronic) or AAD (Class I or III). Symptoms and QoL were assessed at baseline, 1, 3, 6, 9, and 12 months using the EHRA classification and Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT) and SF-36v2 questionnaires. Symptomatic palpitations were evaluated via patient diary.

Results Overall, 107 patients were randomized to CBA and 111 to AAD; crossovers occurred in 9%. Larger improvements in the AFEQT summary, subscale and treatment satisfaction scores were observed at 12 months with CBA vs AAD (all $P < 0.05$). At 12 months, the mean adjusted difference in the AFEQT summary score was 9.9 points higher in the CBA group (95% CI: 5.5 –14.2, $P < 0.001$). Clinically important improvements in the SF-36 physical and mental component scores were observed at 12 months in both groups, with no significant between group differences at this timepoint. In the CBA vs AAD group, larger improvements in EHRA class were observed at 6, 9 and 12 months ($P < 0.05$) and the incidence rate of symptomatic palpitations was lower (4.6 vs 15.2 days/year post-blanking; IRR: 0.30, $P < 0.001$).

Conclusions In patients with symptomatic AF, first-line CBA was superior to AAD for improving AF-specific QoL and symptoms.

Trial registration ClinicalTrials.gov number: NCT01803438. (Am Heart J 2021;242:103–114.)

The primary indication for rhythm control therapy in atrial fibrillation (AF) patients is to reduce arrhythmia-related symptoms and improve quality of life (QoL).[1] Antiarrhythmic drugs (AADs) are the predominant first-line rhythm control strategy in patients with symptomatic AF, while catheter ablation is recommended in patients who are intolerant or non-responsive to at least one AAD in current guidelines.[1-3] Increasing evidence supporting a benefit of early intervention with catheter ablation has raised questions around the optimal timing for the procedure.[4-7] Additionally, ablation has been found to be superior to AADs for preventing atrial arrhythmia recurrence when used as an initial first-line rhythm control strategy

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in drug naïve patients,[8-11] suggesting that there may be clinical benefit to ablation prior to failure of AAD therapy. However, the impact of first-line treatment with catheter ablation (especially cryoballoon ablation; CBA) on QoL and symptoms has not been well characterized.

To date, three randomized trials have evaluated radiofrequency (RF) ablation versus AAD therapy as a first-line treatment in patients with symptomatic paroxysmal AF.[12-14] 2 of these three studies observed a larger improvement in select components of general QoL measures with RF ablation.[12,14] More recently, the EARLY-AF trial evaluated first-line CBA vs AAD therapy and demonstrated larger improvements in both AF-specific and general QoL measures with CBA.[8] These 4 previous studies also suggest that first-line catheter ablation is superior to initial treatment with AAD therapy for reducing symptomatic AF [12,14] or atrial arrhythmia [8,13] recurrence.

Cryo-FIRST was a prospective randomized trial evaluating CBA vs AAD therapy in patients undergoing initial rhythm control therapy for symptomatic paroxysmal AF.[10] This current analysis presents the impact of pulmonary vein isolation (PVI) using CBA compared to AAD therapy on symptom recurrence and QoL.

Methods

Trial design

Cryo-FIRST (NCT01803438) was a multicenter, prospective, open blind-endpoint, controlled randomized (1:1) study evaluating PVI using CBA vs AAD therapy in patients naïve to rhythm-control with symptomatic paroxysmal AF. Detailed methods of the Cryo-FIRST trial have been previously published.[15] The primary endpoint was atrial arrhythmia recurrence >30 seconds outside of a 90-day blanking period. Evaluation of QoL and symptomatic palpitation burden were secondary endpoints. The study complied with the Declaration of Helsinki and ISO 14155. Local ethics review committees approved the study at each participating center, and all patients provided written informed consent prior to participating in the study. The study was sponsored and funded by Medtronic, B.V. A steering and publication committee composed of experienced physicians provided oversight in the design and conduct of the study. The authors are fully responsible for all study analyses, the drafting and editing of the paper and its final contents.

Study participants

A complete list of all inclusion and exclusion criteria has been previously published.[15] In summary, patients 18 to 75 years old with recurrent symptomatic paroxysmal AF were enrolled at 18 centers in Europe, Australia and Argentina. All patients were drug naïve (had not previously received a Class I or III AAD for > 48 hours) and had no history of a left atrial ablation (percutaneous or surgical). Patients were also required to have a normal ECG as well as a structurally normal heart (defined as left ventricular ejection fraction ≥50%, thickness of the interventricular septum ≤12 mm and short-axis left atrium diameter <46 mm). After enrollment, patients were randomized (1:1) to undergo PVI using CBA or AAD therapy.

Cryoballoon catheter ablation

The CBA procedure has been previously described in detail.[10,15] In brief, a second-generation cryoballoon (Arctic Front Advance Cardiac Cryoablation Catheter, Medtronic) was delivered using a transseptal puncture and an over-the-wire delivery technique. The balloon was placed at the antral pulmonary vein (PV) location with the goal of PV occlusion before each freeze application. Acute PVI was confirmed by entrance block (and where assessable, exit block) testing using a dedicated inner lumen, circular diagnostic mapping catheter (Achieve Mapping Catheter, Medtronic) or a lasso-style diagnostic catheter. Patients were discharged and maintained on systemic anticoagulation therapy for a minimum of 3 months. Repeat ablation and use of AADs were allowed during the first 90 days after the index procedure. After the 90-day blanking period, all class I and III AADs were discontinued, and repeat ablation was defined as a primary endpoint failure.

AAD therapy

Class I or III AADs (avoiding amiodarone) were used in accordance with ESC guidelines. Guideline-based AAD dosing recommendations included: flecainide 100 –200mg twice daily or 200mg once daily (slow release); propafenone 150 –300mg 3 times a day or 225 –425mg twice daily (extended release); dronedarone 400mg twice daily; or sotolol 80 –160mg twice daily.[16] Drug, dose, and schedule changes were permitted during the 90-day blanking period.

Symptom evaluation

All patients received a daily diary to document symptomatic palpitation occurrence and duration. Symptom data were reviewed at in-person follow-up visits that occurred at 1, 3, 6, 9, and 12 months. In addition, the European Heart Rhythm Association (EHRA) classification was used to quantify symptoms related to AF at baseline and each follow-up visit. EHRA class I represents no symptoms, class II represents mild symptoms where daily activities are not affected, class III represents severe symptoms where normal daily activity is affected and class IV represents disabling symptoms where normal daily activity is discontinued.

Quality of life measures

QoL was evaluated at baseline, 1, 3, 6, 9, and 12 months using the Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT) questionnaire and SF-36v2 Health Survey. The AFEQT is a self-administered AF-specific health-

related QoL questionnaire that provides a treatment satisfaction score, a summary score and 3 subscale scores (symptoms, daily activities and treatment concerns). Scores range from 0 (complete AF-related disability) to 100 (no AF-related disability). The SF-36 is a generic indicator of health status, and includes 2 summary scores (the physical component score [PCS] and mental component score [MCS]) based on eight health domains (physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional health problems, and mental health). Higher scores indicate better health.

Clinically important differences were considered to be 5 points for the AFEQT summary and subscale scores.[17] For the SF-36, the following were considered to be clinically important point differences for group mean scores: PCS – 2; MCS – 3; physical functioning – 3; role-physical – 3; bodily pain – 3; general health – 2; vitality functioning – 2; social functioning – 3; role-emotional – 4; and mental health – 3 points.[18]

Statistical analysis

Responses on the AFEQT questionnaire were scored on a 1 to 7 Likert scale. The overall AFEQT summary score was calculated using the formula: 100-[((sum of severity for all questions answered-number of questions answered)*100)/(total number of questions answered*6)]. Subscale scores were calculated using the same formula, but only including the specific subset of questions related to each subscale. Total raw scores for each health domain of the SF-36 were calculated and transformed to 0 –100 scores. Health domain 0 –100 scores were then transformed to norm-based T-scores (based on the US Quality Metric 2009 Norming Study) so that each scale had an average of 50 and a standard deviation of 10. MCS and PCS scores were calculated using the T-scores for each health domain.

Primary analyses were based on the intention-to-treat (ITT) cohort. A sensitivity analysis was performed in a per-protocol cohort that included all subjects randomized until the point of crossover. The change in QoL over time was analyzed by means of mixed models for continuous outcomes to account for repeated measures using patient as the subject, QoL scores as the dependent variable and treatment group, baseline values, and visits (time) as explanatory variables. Differences in the rate of days with recurrent symptomatic palpitations occurring after the 90-day blanking period were estimated and compared between groups by means of the mixed Poisson model. Group differences in the change in EHRA class from baseline to each follow-up visit were assessed using the Mann-Whitney U Test. No adjustments for multiple comparisons were performed, and missing data were not imputed.

Results

Patients and treatment characteristics

Subject baseline characteristics are presented in (Table I). The ITT cohort consisted of 107 patients randomized to CBA and 111 patients randomized to AAD therapy. A total of 96 of 107 patients (96.4%) randomized to CBA underwent PVI, and 103 of 111 subjects (92.8%) randomized to AAD therapy initiated drug treatment. The 12-month follow-up was completed by 187 subjects (85.8%). A total of 6 subjects in the CBA arm underwent six repeat ablations, four of which occurred during the blanking period. No patients in the CBA group who underwent an ablation received class I or III AADs after the end of the 90-day blanking period. There was a total of 20 crossovers (9% of subjects); 19 subjects in the AAD arm underwent catheter ablation during follow-up, and 1 subject in the CBA arm chose not to undergo an ablation and received AAD therapy. AAD use was discontinued in 20 patients randomized to AAD therapy due to cross over to ablation ($n = 17$ out of 19 patients who crossed over), patient non-compliance ($n = 1$), patient withdrawal from the study ($n = 1$) and physician discretion secondary to the development of AAD-related side effects ($n = 1$).

AFEQT

A total of 89 patients randomized to CBA (83.2%) and 92 patients randomized to AAD (82.9%) completed the AFEQT survey at baseline and 12 months of follow-up. In the ITT analysis, there was no difference in the AFEQT summary, subscale or treatment satisfaction scores between groups at baseline (Figure 1A, Table II). The adjusted mean AFEQT summary score was significantly higher in the CBA vs AAD arm at 3, 6, 9 and 12 months, and the adjusted mean difference was clinically important (>5 points)[17] at these timepoints (Figure 1B). At 12 months, the mean adjusted difference was 9.9 points higher in the CBA arm (95% CI: 5.5 – 14.2, $P < 0.001$). The AFEQT subscale and treatment satisfaction scores were also more favorable in the CBA vs AAD arm at 12 months (Table II). Similar findings were observed in the per-protocol analysis (Supplement Table I).

To assess the association between atrial arrhythmia recurrence and QoL, the 12-month change in AFEQT was evaluated in patients with vs without atrial arrhythmia recurrence post-blanking in each treatment arm. In the CBA group, the mean 12-month change in AFEQT was 21.0±23.1 in patients with atrial arrhythmia recurrence post-blanking vs 28.5±19.9 in patients without recurrence. In the AAD group, the mean 12-month change in AFEQT was 20.2±23.1 in patients with recurrence vs 17.4±9.4 in patients without recurrence.

Table I. Baseline subject characteristics

	CBA (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 enrollment, 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%)
Coronary artery disease	2 (1.9%)	1 (0.9%)
Valve dysfunction	3 (2.8%)	2 (1.8%)
CHA_2DS_2VASc 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%)
Beta blocker	54 (50.5%)	56 (50.5%)
Calcium channel blocker	9 (8.4%)	15 (13.5%)

Values are n (%) or mean (standard deviation).
CBA, cryoballoon ablation. AAD, antiarrhythmic drug. AF, atrial fibrillation. EHRA, european heart rhythm association score. $CHARR_2RRDSRR_2RR$-VASc Score, congestive heart failure, hypertension, age ≥75 [doubled], diabetes mellitus, prior stroke or transient ischemic attack [doubled], vascular disease, age 65 –74, female).
*Data are unavailable for 2 subjects in the AAD arm

SF-36 summary scores

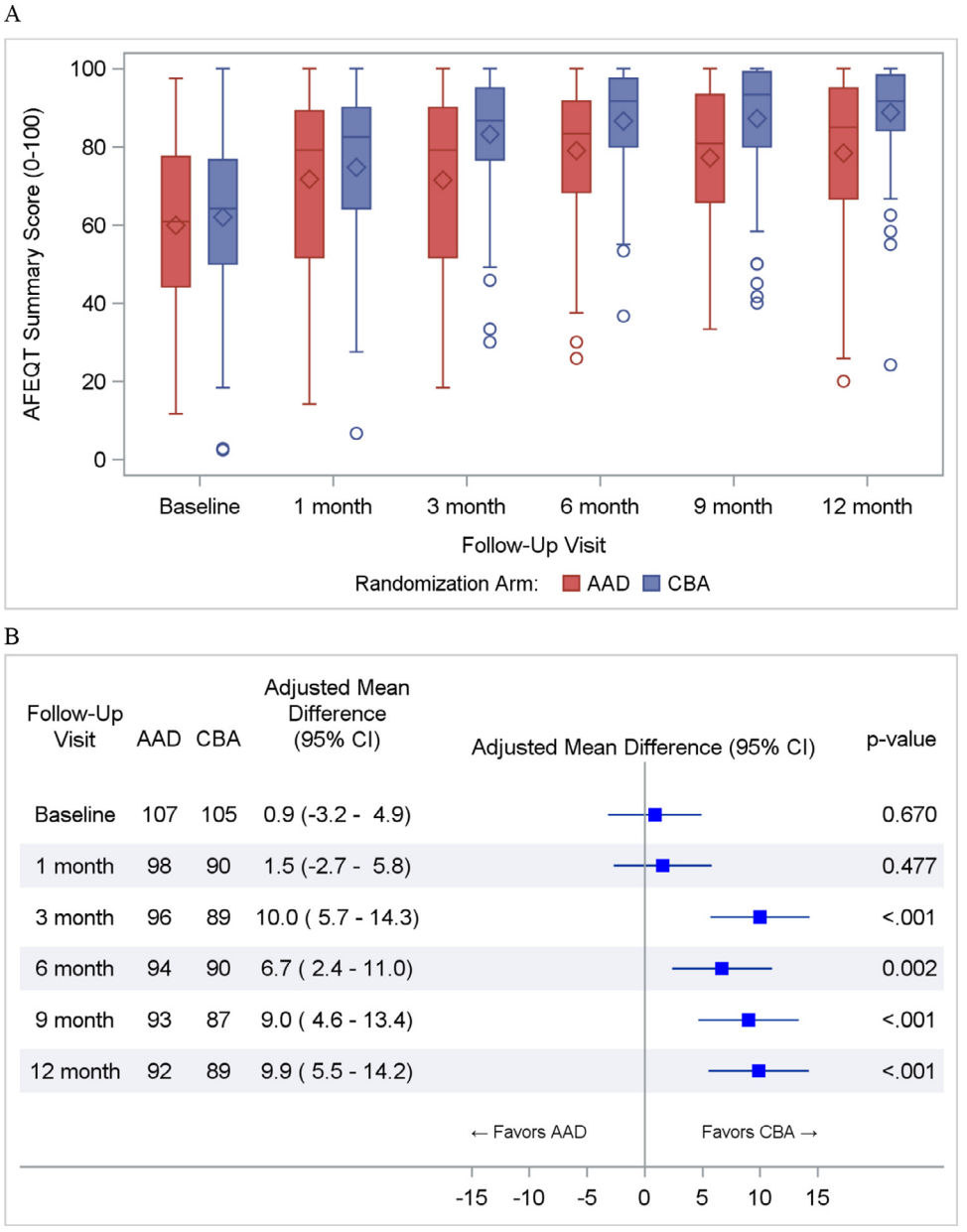
A total of 90 patients randomized to CBA (84.1%) and 90 patients randomized to AAD (81.1%) completed the SF-36 survey at baseline and 12 months of follow-up. The PCS improved from 50.1±7.5 to 54.1±6.4 with CBA and from 48.0±8.0 to 51.9±7.9 with AAD therapy (Figure 2A, Table II). In both groups, the improvement at 12 months exceeded the clinically important difference (2 points) for this score.[18] The adjusted mean difference between groups was not statistically significant at 12 months. However, the PCS was significantly higher in the CBA vs. AAD arm at 3 and 9 months, with a clinically important difference observed between groups at the 9-month timepoint (Figure 2B). Findings were similar in the per-protocol analysis, with statistically significant group difference favoring CBA observed in the PCS score at 3 and 9 months (Supplemental Figure 1).

The MCS improved from 46.3±9.6 at baseline to 49.8±9.1 at 12 months in the CBA arm and from 44.0±10.8 at baseline to 47.5±9.8 at 12 months in the AAD arm (Table II). The improvement in the MCS exceeded the clinically important difference (3 points) in both groups. There were no significant group differences in the MCS at baseline or at any follow-up visit in the ITT (Figure 2C and D) or per-protocol analysis (Supplemental Figure 2).

SF-36 health domain scores

The SF-36 norm-based health domain scores at baseline and 12 months in the ITT analysis are shown in (Figure 3). Compared to baseline measurements, improvements were observed in all health domains at 12 months within both the CBA and AAD arms. In the CBA arm, improvements at 12 months exceeded the clinically important difference for all domains except role-emotional. In the AAD arm, 12-month improvements exceeded the clinically important difference for all domains except physical functioning and role-emotional. There were no significant between group differences in any of the health domain scores at 12 months in the ITT analysis (Table II). In the per-protocol analysis, the mean adjusted difference at 12 months was significantly higher in the CBA group for three health domains (physical functioning, general health and social functioning; (Supplement Table II). Non-normalized 0-100 scores at baseline and 12 months are presented in Supplemental Table III.

Figure 1



AFEQT summary scores in the intention to treat cohort. **Panel A**, Box plot showing AFEQT summary score at each follow-up. Boxes indicate the interquartile range (IQR), with the mid-line representing the median and the diamond representing the mean. Whiskers extend from each box to the farthest point within ±1.5 times the IQR. Values outside this range are considered outliers and denoted by circles or plus signs. **Panel B,** Forest plot showing the adjusted mean difference in the AFEQT summary score at each follow-up visit.

Symptoms

After the blanking period, 30 of 107 subjects in the CBA arm (28.0%) experienced 307 days with palpitations and 49 of 111 subjects in the AAD arm (44.1%) experienced 1042 days with palpitations (4.6 vs 15.2 days per year, respectively; incidence rate ratio: 0.30, P <0.001). In addition, the daily duration of palpitations after blanking was shorter in the CBA (54.4±131.1 minutes) vs the AAD arm (102.7±162.8 minutes).

EHRA class at baseline is shown in (Table I). Significantly larger improvements in EHRA class were observed in the CBA vs AAD arm at 6, 9 and 12 months (Figure 4).

Table II. AFEQT and SF-36 scores at baseline and 12 months in the intention-to-treat cohort

	CBA		AAD		Adjusted mean difference at 12 months (CBA vs AAD)	*P*-value
	Baseline	12 Months	Baseline	12 Months		
AFEQT score, mean ± standard deviation						
Summary score	62.0 ± 19.5	88.9 ± 12.8	59.9 ± 20.6	78.1 ± 19.8	9.9 (5.5 – 14.2)	<0.001
Daily activities	65.3 ± 25.8	87.8 ± 17.1	61.0 ± 27.9	76.6 ± 25.4	8.9 (3.2 – 14.6)	0.002
Symptoms	59.9 ± 24.8	88.8 ± 15.6	58.4 ± 25.2	80.9 ± 22.2	7.1 (1.5 – 12.7)	0.014
Treatment concern	59.9 ± 23.1	89.8 ± 14.0	60.4 ± 24.5	77.7 ± 22.2	12.7 (7.9 – 17.5)	<0.001
Treatment satisfaction	59.9 ± 24.2	90.6 ± 14.2	56.2 ± 28.7	79.8 ± 20.7	10.2 (4.1 – 16.2)	<0.001
SF-36 score, mean ± standard deviation						
Physical component	50.1 ± 7.5	54.1 ± 6.4	48.0 ± 8.0	51.9 ± 7.9	1.0 (-0.7 – 2.6)	0.244
Mental component	46.3 ± 9.6	49.8 ± 9.1	44.0 ± 10.8	47.5 ± 9.8	0.2 (-1.8 – 2.3)	0.833
Health domain scores						
Physical functioning	50.7 ± 7.6	54.1 ± 6.4	48.9 ± 8.5	51.0 ± 8.4	1.8 (-0.1 – 3.6)	0.060
Role-physical	46.7 ± 8.5	50.7 ± 7.5	43.4 ± 9.6	48.2 ± 9.2	0.5 (-1.5 – 2.4)	0.646
Bodily pain	50.7 ± 11.2	54.0 ± 8.8	47.4 ± 11.2	52.2 ± 10.7	0.0 (-2.3 – 2.4)	0.968
General health	47.7 ± 8.9	52.8 ± 9.1	47.3 ± 9.2	51.3 ± 9.2	1.0 (-0.8 – 2.9)	0.281
Vitality functioning	49.1 ± 9.1	54.5 ± 8.7	47.8 ± 9.9	52.2 ± 9.5	1.1 (-1.0 – 3.2)	0.294
Social functioning	47.6 ± 9.4	51.3 ± 7.1	44.3 ± 10.8	47.7 ± 9.3	1.4 (-0.8 – 3.5)	0.213
Role-emotional	47.1 ± 9.4	49.4 ± 8.7	43.0 ± 11.4	46.6 ± 10.7	0.1 (-2.1 – 2.3)	0.928
Mental health	46.4 ± 9.2	50.3 ± 9.4	45.3 ± 10.2	48.6 ± 10.2	0.3 (-1.8 – 2.4)	0.774

CBA, cryoballoon ablation. AAD, antiarrhythmic drug. SF-36 norm-based health domain scores are shown.

At 12 months in the CBA group, 86.5% of subjects were EHRA class I, 9.0% were EHRA class II and 4.5% were EHRA class III. In the AAD arm, 70.4% of subjects were EHRA class I, 24.5% were EHRA class II and 5.1% were EHRA Class III.

Discussion

In this multi-center randomized trial of symptomatic paroxysmal AF patients receiving initial rhythm control therapy, both CBA and AAD treatment resulted in improvements in AF-specific and generic measures of QoL. Notably, clinically important group differences in AF-specific health-related QoL were observed, with higher scores in the CBA group at 3 – 12 months of follow-up. After the blanking period, the incidence of days with symptomatic palpitations was 70% lower in the CBA arm. Also, larger improvements in the EHRA class were observed with CBA versus AAD therapy at 6, 9 and 12 months. Together these findings demonstrate a benefit for first-line CBA compared to AAD therapy for improving AF-specific QoL and symptoms in patients with paroxysmal AF.

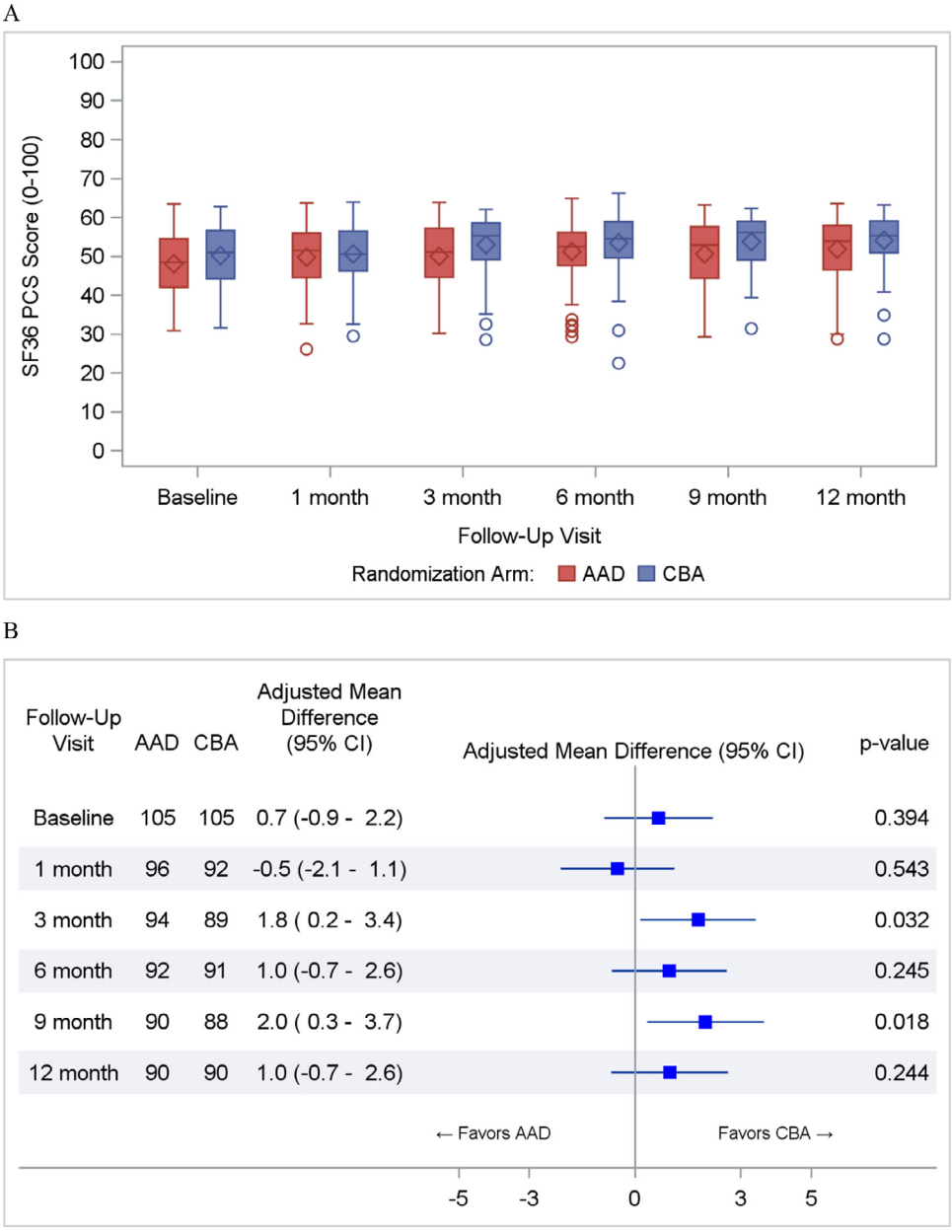
While previous trials have demonstrated that catheter ablation is superior to AAD for preventing atrial arrhythmia recurrence as a first-line rhythm control strategy,[8-11] the primary indication for rhythm control remains the reduction of symptoms and improvement in QoL.[1-3] In the present study, AF-specific QoL improved substantially in both the CBA and AAD groups. However, larger improvements in the AFEQT summary score were seen with CBA starting at 3 months, and this was maintained throughout 12-months of follow-up. Additionally, larger improvements in all AFEQT subscale scores were observed with CBA at 12 months. Although clinically important between group differences were observed in AF-specific QoL, the between group differences were smaller than the overall improvement seen with rhythm control therapy in general.

These findings build on those recently reported by EARLY-AF, the only previous first-line ablation study to evaluate differences in AF-specific QoL in patients treated with CBA vs AAD therapy. At 12 months, this study observed an average 8 point better improvement in the AFEQT summary score with ablation,[8] representing a clinically important difference between groups.[17] Despite the Cryo-FIRST and EARLY-AF patient populations being fairly early in the AF disease process, the 12-month improvement in the AFEQT summary score with CBA in these trials (27 points in both the present study and in EARLY-AF) is similar to that previously reported in drug-refractory paroxysmal and persistent AF patients (26 – 32 point improvement)[19,20]

In the present trial, the mean 12-month change in AFEQT was numerically higher in CBA patients who did not have atrial arrhythmia recurrence vs those that did.

Interestingly, this was not observed in the AAD group, where the 12-month change in AFEQT was similar in patients with and without atrial arrhythmia recurrence during follow-up. In patients randomized to AAD who did not have atrial arrhythmia recurrence detected during follow-up, improvements in QoL may have been diminished due to anxiety around drug therapy, lack of adequate symptom control, and/or development of drug side effects.[21]

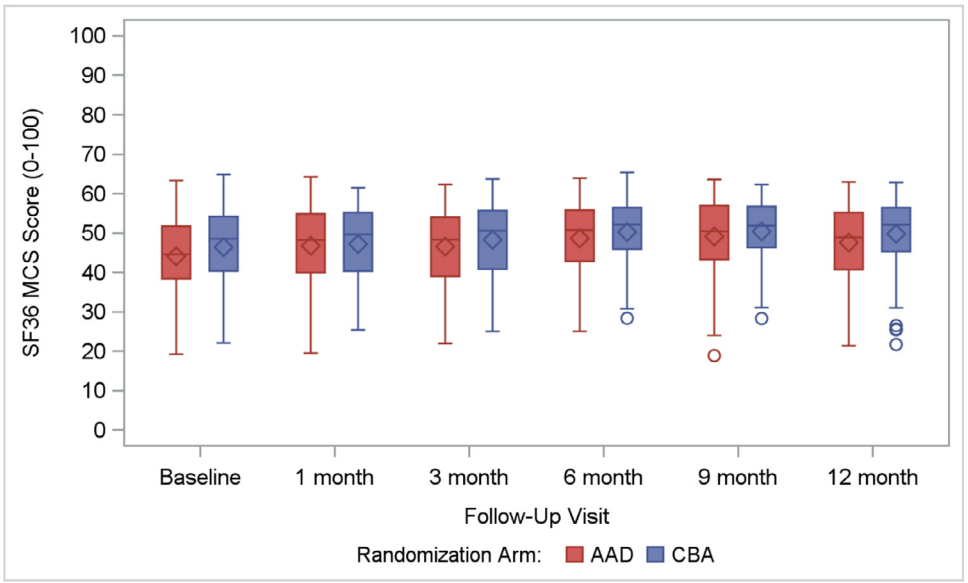
Figure 2



SF-36 summary scores in the intention to treat cohort. **Panel A,** Box plot showing the physical component score (PCS) at each follow-up visit **Panel B,** Forest plot showing the mean adjusted difference in the PCS at each follow-up visit **Panel C,** Box plot showing the mental component score (MCS) at each follow-up visit **Panel D,** Forest plot showing the mean adjusted difference in the MCS at each follow-up visit

Figure 2

C



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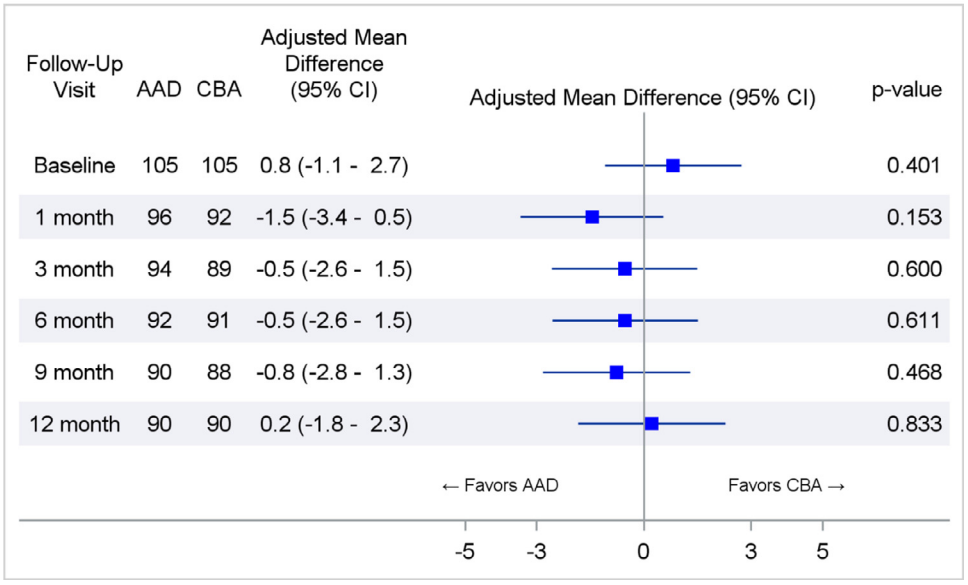
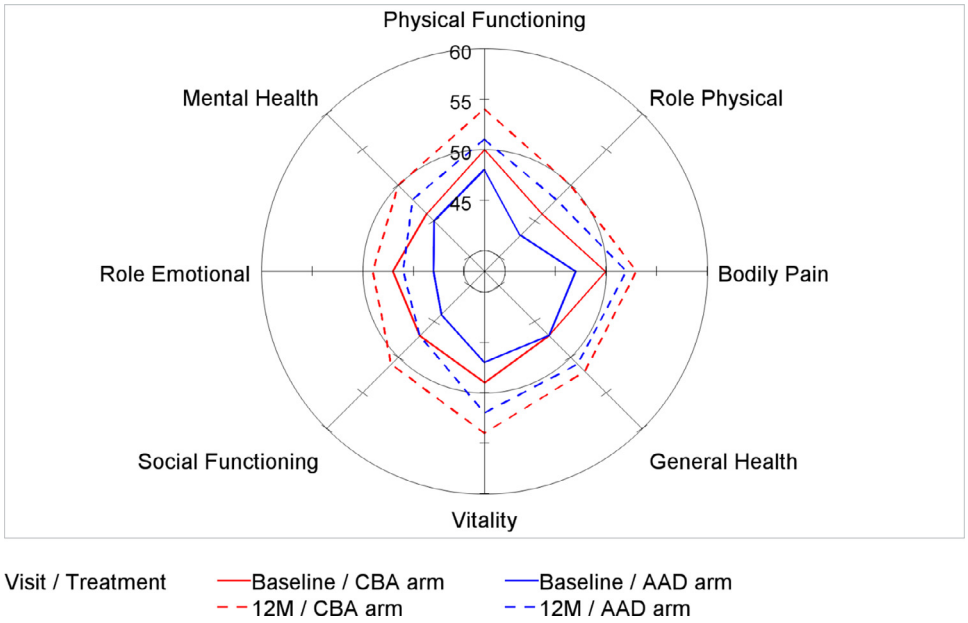


Continued

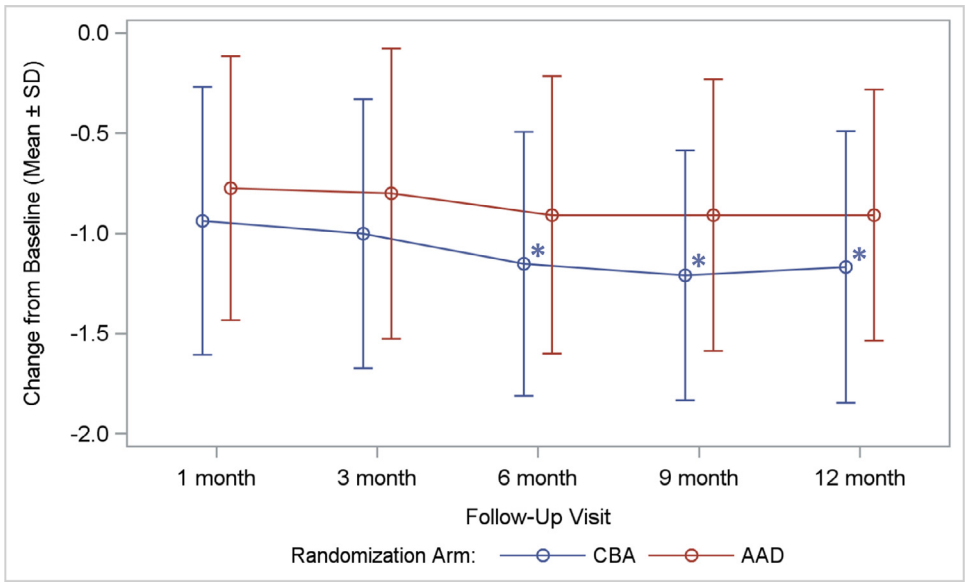
Generic QoL instruments have been more broadly used in randomized studies comparing ablation to AAD therapy as a first-line treatment; however, findings have been inconsistent. 2 prior studies evaluating first-line RF ablation vs AAD therapy have found improvements in some SF-36 domain scales[14] and in the SF-36 PCS but not MCS [12] with RF ablation. In contrast, a third study reported no significant group differences between first-line RF ablation versus AAD therapy when evaluating QoL with the European Quality of Life–5 Dimensions (EQ-5D) questionnaire.[13] More recently, EARLY-AF reported a clinically important treatment effect in favor of first-line CBA for the EQ-5D index, but not visual analogue score.[8] Finally, the CAPTAF trial observed larger improvements in 6 of 8 SF-36 health domain scales with catheter ablation (using either RF or CBA) compared to AAD treatment.[22]

Figure 3



Star chart showing the norm-based T scores for the 8 SF-36 health domains at baseline and 12 months in the cryoballoon ablation (CBA, red) and anti-arrhythmic drug (AAD, blue) groups. Each axis represents a different SF-36 health domain and displays scores on a range from 40-60.

Figure 4



Mean change in the European Heart Rhythm Association (EHRA) classification at each follow-up visit. A reduction in EHRA class represents less severe symptoms. *P <0.05 vs AAD arm at the same time point.

Over half the patients in this trial had only failed beta-blockers before enrollment, representing a population similar to that enrolled in the aforementioned first-line ablation studies.

In the present investigation, clinically important improvements in the SF-36 PCS and MCS were observed at 12 months in both the CBA and AAD group. However, the magnitude of improvement in the PCS and MCS following first-line CBA was smaller than what has been observed following catheter ablation in drug-refractory populations.[23,24] In addition, there were no significant between group differences in either the PCS or MCS at 12 months. The per-protocol analysis did demonstrate significantly greater improvements in three health domains at 12 months, including general health, with CBA. The less consistent benefit of ablation compared to AAD therapy for improving generic versus AF-specific QoL measures in Cryo-FIRST and previous first-line ablation studies may reflect the lower sensitivity of generic QoL tools (more blunt instruments) to detect changes in AF-specific health status.[2,25] Since these questionnaires are designed to reflect general health and functioning, measurements can be significantly impacted by patient demographics and comorbidities unrelated to the study intervention.[26] In contrast, AF-specific QoL instruments (more specific tools) include domains that are relevant and specific to AF, increasing the sensitivity to detect changes in AF-related health status.[25] Indeed, the AFEQT questionnaire has been shown to be more responsive to rhythm-control therapies for AF than the SF-36 questionnaire.[27]

A key objective of rhythm control is to reduce AF-associated symptoms.[1-3] Prior first-line studies using RF ablation have reported lower rates of symptomatic AF[12,14] or atrial arrhythmia recurrence [13] with ablation versus AAD therapy, and more recently, EARLY-AF demonstrated a reduction in symptomatic atrial arrhythmia recurrence with first-line CBA compared to AAD treatment.[8] Additionally, both EARLY-AF and Cryo-FIRST observed a larger proportion of asymptomatic patients in the CBA vs AAD group at the end of follow-up.[8,10] In the present analysis of the Cryo-FIRST trial, the incidence of days with patient-reported symptomatic palpitations outside of the blanking period was 70% lower in the CBA group. Moreover, the daily duration of palpitations after blanking in the CBA group was approximately half of that reported in the AAD group. Finally, a larger mean improvement in EHRA class was observed with CBA versus AAD therapy at 6 through 12 months. These findings further support the benefit of first-line ablation for reducing symptom recurrence in patients with paroxysmal AF.

Patients with symptomatic AF frequently report that symptoms cause anxiety, impact their activities of daily living, and generate worry for relatives, which can negatively impact social relationships.[21] Furthermore, symptoms are a major cause of healthcare utilization in patients with AF.[28] As such, improved symptom relief with CBA vs AAD therapy in patients with drug naïve symptomatic paroxysmal AF may have significant socioeconomic benefits. Understanding patient perception of health and wellbeing is critical to comprehensively evaluate the impact of different rhythm control strategies, especially when considering that patient experience does not always correlate with objective measures of disease severity.[29] Indeed, we did not observe a strong association between QoL improvements and atrial arrhythmia recurrence in the drug arm in the present investigation.

Limitations

Our trial has some limitations. Although this was a randomized study and patients were assigned to each treatment by chance, there may have been modest group imbalances in baseline subject characteristics due to the relatively small sample size. This study was not blinded, and QoL measures may have been subject to treatment expectancy bias; however, sham ablation procedures pose ethical concerns.[2] Crossovers occurred in 9% of patients, primarily from the AAD to cryoballoon arm, which may have diminished group differences in QoL. Indeed, the per-protocol analysis demonstrated larger group differences in QoL improvements with both the AFEQT and SF-36 instruments. Patients were only followed for 12 months and longer follow-up periods are needed to determine the lasting impact of first-line CBA vs AAD therapy on QoL and AF-symptoms. Importantly, frequent crossovers from AAD to ablation pose a challenge for extended follow-up periods. Lastly, we were not able to correlate the recurrence of symptomatic palpitations to atrial arrhythmia recurrence. However, as the primary indication for rhythm control therapy is the management of symptoms, patient perception of AF-symptoms as documented in patient diaries is a clinically important endpoint.

Conclusion

In summary, improvements in QoL were observed with both CBA and AAD treatment in patients with symptomatic paroxysmal AF undergoing initial rhythm control therapy. CBA resulted in clinically important and sustained improvements in AF-specific QoL compared to AAD treatment. In addition, a lower incidence of symptomatic palpitations post-blanking, and larger improvement in EHRA class were observed with CBA. Together, these findings suggest that CBA with the Arctic Front Advance catheter is an effective first-line rhythm control strategy for improving AF-specific QoL and symptoms.

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Conflict of interest

N. Pavlovic reports speaker's honoraria from Medtronic and Biosense Webster; proctoring fees from Medtronic, Biosense Webster and Abbott. **G. B. Chierchia** reports speaker fees for Medtronic, Biotronik, Biosense Webster, Abbott; teaching honoraria from Medtronic, Biotronik; proctoring honoraria from Medtronic. **V. Velagic** reports speaker fees and proctoring honoraria for Medtronic, travel grants from Biotronik, Biosense-Webster and Medtronic. **J. S. Hermida** reports honoraria for inclusion of patients and realization of the study. S. Healey reports speaker fees for Medtronic, Biotronik, Biosense Webster, Abbott; teaching honoraria from Medtronic, Biotronik; proctoring honoraria from Medtronic. **G. Arena** reports research support on Holter monitors. **N Badenco** reports consultancy fees from Bisosense Webster, Boston Scientific SAS, and Medtronic. C Meyer reports consultancy and speaker fees from Biosense Webster and Boston Scientific. J. Chen reports a research grant from Medtronic. S. Iacopino has no conflicts of interest to declare. F. Anselme reports consultant for and lecture fees from Boston Scientific, Medtronic, Microport. CRM. L. Dekker reports research funding, speaker and consultancy fees from Medtronic and Philips. **F. Scazzuso** reports speaker's honoraria from Medtronic, Abbott and Biosense Webster, and proctoring fees from Medtronic. D. Packer in the past 12 months has provided consulting services for Abbott $0, Biosense Webster $0, Inc., Biotronik <$5000, Boston Scientific $0, CardioFocus $0, Johnson & Johnson $0, MediaSphere Medical, LLC<$5000, Medtronic $0, St. Jude Medical $0, and Siemens $0, SigNum Preemptive Healthcare, Inc.$0, Spectrum Dynamics $0, and Thermedical $0. Dr. Packer receives research funding from the Abbott, Biosense Webster, Boston Scientific/EPT, CardioInsight, CardioFocus, Endosense, German Heart Foundation, Hansen Medical, Medtronic, NIH, Robertson Foundation, St. Jude Medical, Siemens and Thermedical. Mayo Clinic and Dr. **D. Packer** and R. Robb have a financial interest in mapping technology. In accordance with the Bayh-Dole Act, this technology has been licensed to St. Jude Medical, and Mayo Clinic and Drs. Packer and Robb have received annual royalties greater than $10,000, the federal threshold for significant financial interest. Mayo Clinic and Dr. R. Robb have a financial interest in Analyze-AVW technology that may have been used to analyze some of the heart images in this research. In accordance with the Bayh-Dole Act, this technology has been licensed to commercial entities, and both Mayo Clinic and Dr. Robb have received royalties greater than $10,000, the federal threshold for significant financial interest. In addition, Mayo Clinic holds an equity position in the company to which the AVW technology has been licensed. Dr. Packer and Mayo Clinic jointly have equity in a privately held company, External Beam Ablation Medical Devices. **F. Di Piazza** and **R. Kaplon** are employed by and stockholders of Medtronic. **M. Kuniss** reports speaker fees from Abbott and Medtronic; proctoring, consultancy and advisory board services for Medtronic; research grants from Medtronic and Biosense Webster.

Author contributions

N. Pavlovic: investigation, writing – original draft, project administration;**G. B. Chierchia**: conceptualization, methodology, investigation, writing – original draft, supervision, project administration; **V. Velagic**: investigation, writing – review and editing, project administration: **S. Hermida**: conceptualization, methodology, investigation, writing – review and editing, supervision, project administration; **S. Healey**: investigation, writing – review and editing; **G. Arena**: investigation, writing – review and editing; **N. Badenco**: investigation, writing – review and editing; **C. Meyer**: investigation, writing – review and editing; **J. Chen**: investigation, writing – review & editing; **S. Iacopino**: investigation, writing – review and editing; **F. Anselme**: investigation, writing – review and editing; **L. Dekker**: investigation, writing – review and editing; **F. Scazzuso**: investigation, writing – review and editing; **D. Packer**: conceptualization, methodology, writing – review and editing, supervision; **F. Di Piazza**: formal analysis, visualization, writing – review and editing; **R. Kaplon**: writing – original draft, visualization; **M. Kuniss**: conceptualization, methodology, investigation, writing – review and editing, supervision, project administration.

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Data availability

The data underlying this article cannot be shared publicly due to privacy of the individuals that participated in the study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2021.08.007.

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