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Effect of Catheter Ablation vs Antiarrhythmic Medication on Quality of Life in Patients With Atrial Fibrillation
The CAPTAF Randomized Clinical Trial

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IMPORTANCE Quality of life is not a standard primary outcome in ablation trials, even though symptoms drive the indication.

OBJECTIVE To assess quality of life with catheter ablation vs antiarrhythmic medication at 12 months in patients with atrial fibrillation.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial at 4 university hospitals in Sweden and 1 in Finland of 155 patients aged 30-70 years with more than 6 months of atrial fibrillation and treatment failure with 1 antiarrhythmic drug or β-blocker, with 4-year follow-up. Study dates were July 2008–September 2017. Major exclusions were ejection fraction <35%, left atrial diameter >60 mm, ventricular pacing dependency, and previous ablation.

INTERVENTIONS Pulmonary vein isolation ablation (n = 79) or previously untested antiarrhythmic drugs (n = 76).

MAIN OUTCOMES AND MEASURES Primary outcome was the General Health subscale score (Medical Outcomes Study 36-Item Short-Form Health Survey) at baseline and 12 months, assessed unblinded (range, 0 [worst] to 100 [best]). There were 26 secondary outcomes, including atrial fibrillation burden (% of time) from baseline to 12 months, measured by implantable cardiac monitors. The first 3 months were excluded from rhythm analysis.

RESULTS Among 155 randomized patients (mean age, 56.1 years; 22.6% women), 97% completed the trial. Of 79 patients randomized to receive ablation, 75 underwent ablation, including 2 who crossed over to medication and 14 who underwent repeated ablation procedures. Of 76 patients randomized to receive antiarrhythmic medication, 74 received it, including 8 who crossed over to ablation and 43 for whom the first drug used failed. General Health score increased from 61.8 to 73.9 points in the ablation group vs 62.7 to 65.4 points in the medication group (between-group difference, 8.9 points; 95% CI, 3.1-14.7; $P = .003$). Of 26 secondary end points, 5 were analyzed; 2 were null and 2 were statistically significant, including decrease in atrial fibrillation burden (from 24.9% to 5.5% in the ablation group vs 23.3% to 11.5% in the medication group; difference −6.8% [95% CI, −12.9% to −0.7%]; $P = .03$). Of the Health Survey subscales, 5 of 7 improved significantly. Most common adverse events were urosepsis (5.1%) in the ablation group and atrial tachycardia (3.9%) in the medication group.

CONCLUSIONS AND RELEVANCE Among patients with symptomatic atrial fibrillation despite use of antiarrhythmic medication, the improvement in quality of life at 12 months was greater for those treated with catheter ablation compared with antiarrhythmic medication. Although the study was limited by absence of blinding, catheter ablation may offer an advantage for quality of life.

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Visual Abstract

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The indication for catheter ablation in atrial fibrillation is symptomatic, drug-refractory arrhythmia.[1,2] Despite the symptom-driven indication, randomized trials comparing pulmonary vein isolation and antiarrhythmic medication to treat atrial fibrillation have used rhythm-based primary end points,[3-6] most frequently a 30-second atrial fibrillation episode.[7-10] No trials have used symptom or quality-of-life measures as primary end points, to our knowledge. Another important limitation is the lack of continuous rhythm monitoring by an implantable cardiac monitor, which has precluded assessment of the true effect on atrial fibrillation burden.

These limitations are also true for studies evaluating catheter ablation as a first-line treatment for atrial fibrillation, and their conclusions in regard to treatment efficacy may therefore be limited.[7,9,11] The objective of this study was to compare the effects of 2 treatment strategies, catheter ablation and optimized pharmacologic therapy, in patients with symptomatic atrial fibrillation, using the General Health subscale from the Medical Outcomes Study 36-Item Short-Form Health Survey as the primary end point.

Key Points

Question Is pulmonary vein isolation more effective than optimized antiarrhythmic drug therapy for improving general health in patients with symptomatic atrial fibrillation?

Findings In this randomized clinical trial that included 155 patients with paroxysmal or persistent symptomatic atrial fibrillation despite use of antiarrhythmic medication, the improvement in quality of life at 12 months for those treated with catheter ablation compared with antiarrhythmic medication was 11.9 vs 3.1 points on the 0- to 100-point 36-Item Short-Form Health Survey questionnaire, a difference that was statistically and clinically significant.

Meaning In patients with either paroxysmal or persistent symptomatic atrial fibrillation despite medication, catheter ablation may help improve quality of life.

Methods

Study Design

The CAPTAF study (Catheter Ablation compared with Pharmacological Therapy for Atrial Fibrillation) was a multicenter randomized trial with blinded evaluation of outcomes (PROBE design [prospective, randomized, open-label, blinded end point]) conducted to assess whether a strategy of pulmonary vein isolation was superior to optimized antiarrhythmic medication for improving quality of life in patients with symptomatic atrial fibrillation.

The study was approved by the ethics committee and the Swedish Medical Products Agency and conducted according to the Declaration of Helsinki. All patients gave written informed consent. The trial protocol is available in Supplement 1.

Patient Population

Patients were enrolled between July 2008 and May 2013 at 5 centers in Sweden and Finland. Participant follow-up ended September 28, 2017. Inclusion criteria were age 30 through 70 years, history of symptomatic atrial fibrillation for at least 6 months and verified on electrocardiogram (ECG) in the previous 12 months, at least 1 paroxysmal atrial fibrillation episode in the previous 2 months or 2 persistent atrial fibrillation episodes converted to sinus rhythm in the previous 12 months, and failure of or intolerance to a maximum of 1 antiarrhythmic drug (including β-blockers).

Major exclusion criteria were New York Heart Association class III to IV, left ventricular ejection fraction less than 35%, left atrial diameter greater than 60 mm, previous atrial fibrillation ablation, and ventricular pacing dependency. Other exclusion criteria were atrial fibrillation secondary to a transient or correctable abnormality or triggered by another supraventricular tachycardia, uncontrolled hypertension, valve disease requiring long-term anticoagulation or surgery within 2 years, contraindication to transseptal catheterization, vascular access or treatment with anticoagulants, acute coronary syndrome within the last 3 months, cardiac revascularization within the last 6 months, previous cardiac surgery or planned cardiac surgery within 1 year, kidney dialysis, abnormal liver function test results, lack of informed consent, psychological problem limiting adherence, and active misuse of alcohol or other substance.

Randomization

Patients were randomized after a 2-month run-in period (**Figure 1**). The treatment allocation sequence was generated using permuted block randomization (block size = 4 and 1:1 allocation) stratified by center and type of atrial fibrillation (paroxysmal or persistent). The randomization code was generated by a validated database system.

Implantable Cardiac Monitor for Continuous Rhythm Monitoring

An implantable cardiac monitor (Reveal XT, Medtronic Inc) was implanted after enrollment (except in pacemaker patients with adequate atrial monitoring capacity) for evaluation of atrial fibrillation burden, starting with the 2-month run-in phase as baseline (Figure 1). Because of the device algorithm, data were available only for episodes lasting 2 minutes or longer. The device programming was standardized (eTable 1 in Supplement 2).

Catheter Ablation Strategy

Oral anticoagulation was given at least 4 weeks before and 3 months after ablation. Left atrial thrombi were excluded by transesophageal echocardiography 1 to 2 days before ablation. Heparin or low-molecular-weight heparin was used when bridging was needed. Heparin was given during the procedure as recommended.[2] Circumferential pulmonary vein isolation was performed according to institutional preference, mainly with an open, irrigated-tip, radiofrequency catheter guided by an electroanatomic mapping system or with a cryoballoon. A left atrial roof line was optional in

patients with persistent atrial fibrillation and for reablations. Pulmonary vein entrance block was demonstrated with a circular mapping catheter. Conduction block across the roof line was confirmed by pacing maneuvers. Antiarrhythmic medication continued for 3 months after ablation. Reablation was allowed after the 3-month blanking period (a period of therapeutic stabilization after ablation during which any occurrence of atrial fibrillation is not considered treatment failure or atrial fibrillation recurrence). Antiarrhythmic medication after the blanking period was considered crossover.

Optimized Antiarrhythmic Medication

Optimized antiarrhythmic medication included testing of all available drugs at adequate dosages according to guidelines (protocol in Supplement 1). A change of drug was guided by the patient's symptoms and allowed earliest after 1 month's treatment (3 months for amiodarone). Crossover to ablation was offered at the patient's request if antiarrhythmic medication failed. Physicians were advised to keep patients in the same treatment group for at least 12 months.

Outcome Measures

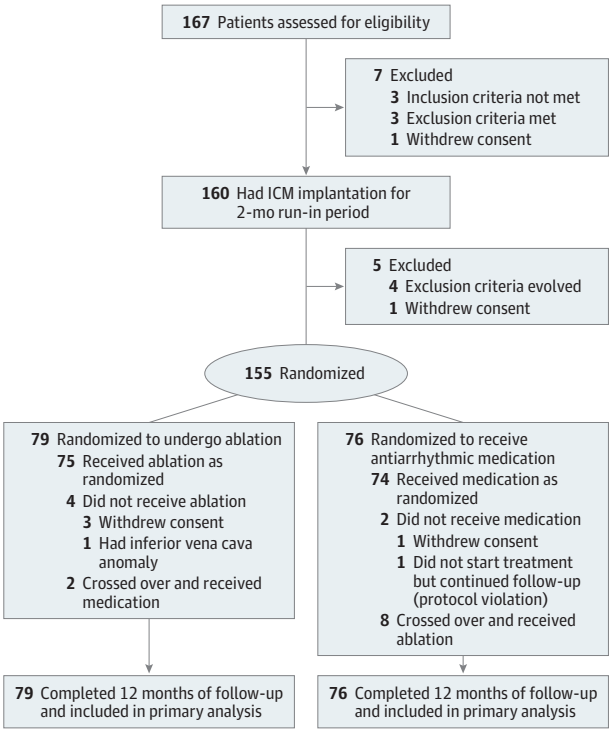
The primary outcome was the General Health subscale score from the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) measured at baseline and at 12 months. For each of the 8 SF-36 subscales, scores were coded and transformed to a scale ranging from 0 to 100 (higher scores indicating greater well-being). A minimal clinically important difference was not calculated. However, according to the SF-36 manual, a 5-point difference is defined as a "clinically and socially relevant" difference, 10 points as a "moderate" one, and 20 points as a "very large" one.[12] The minimal detectable difference for the power calculation is described in the statistical analysis section.

Prespecified secondary outcomes included the remaining 7 SF-36 subscales, European Heart Rhythm Association symptom score, number of cardioversions, atrial fibrillation burden (percentage of time in atrial fibrillation), and freedom from atrial fibrillation recurrence (at least 2 minutes' duration on implantable cardiac monitors and 1 minute on 24-hour Holter recordings).

Prespecified unanalyzed secondary outcomes were a composite of morbidity (embolic events, major bleeding, pacemaker implantation, and all-cause death), all-cause death, success or failure of treatment, hospitalizations, use of antiarrhythmic drugs, left ventricular heart failure, New York Heart Association function class, quality of life by EQ-5D score, symptoms (Symptoms Severity Questionnaire and Disease Related Symptom Questionnaire), patient's estimate of symptomatic episodes, atrial fibrillation profile, left ventricular function and diameters, left and right atrial area and function, exercise capacity, C-reactive protein, N-terminal pro-B-type natriuretic peptide, covariate-adjusted primary end points, health care costs, and baseline predictors for symptom- or rhythm-based response by treatment group.

Post hoc outcomes included a composite of first clinical events related to atrial fibrillation (first cardioversion, cardiovascular-related hospitalization, reablation, and change of antiarrhythmic medication) from baseline to 12-month follow-up, an analysis of general health improvement and its association to reduction in atrial fibrillation burden, and 2 sensitivity analyses of the General Health subscale and the other SF-36 subscales.

Figure 1. Patient Enrollment, Randomization, and Follow-up



Patients were distributed among centers as follows: 49% of patients from Uppsala University hospital, 28% from Sahlgrenska Academy University hospital, 16% from Karolinska University hospital, 7% from Umeå University hospital, and 1% from Tampere University hospital.

The European Heart Rhythm Association score assessed the severity of atrial fibrillation–related symptoms; classes I, II, III, and IV indicate no, mild, severe, and disabling symptoms, respectively, with normal daily activity unaffected (class II), affected (class III), and discontinued (class IV). Rhythm events were not counted during the 90-day blanking period.

Core laboratories analyzed implantable cardiac monitor recordings (at Uppsala University) and 2- to 3-channel digital 24-hour Holter recordings (at Umeå University). Patients and physicians providing care and assessing outcomes were blinded to all rhythm recordings. An independent adjudication committee evaluated the prespecified serious adverse events for their relation to allocated treatments.

Follow-up

Follow-up was scheduled at 3, 6, 9, and 12 months and then every 6 months until 48 months after initiation of randomized therapy. Medical history, physical examination, implantable cardiac monitor interrogation (until battery depletion at

Table 1. Characteristics of the Patients at Baseline

	Ablation (n = 79)	Medication (n = 76)
Age, mean (SD), y	55.8 (10.6)	56.3 (8.9)
Sex, No. (%)		
Male	58 (73.4)	62 (81.6)
Female	21 (26.6)	14 (18.4)
Body mass index, mean (SD)[a]	27.3 (3.6)	26.9 (3.8)
Type of AF, No. (%)		
Paroxysmal	56 (70.9)	57 (75.0)
Persistent	23 (29.1)	19 (25.0)
AF burden, % of time, mean (SD)[b]	24.9 (37.0)	23.3 (36.9)
Median (IQR)	3.7 (0.6-33.1)	3.5 (0.2-26.4)
AF duration by history, median (IQR), y	3.5 (1.6-7.0)	5.6 (1.5-7.6)
AF episodes in last 12 mo, median (IQR)	8.0 (4.0-40.0)	7.5 (3.0-50.0)
Cardioversion last 12 mo, No. (%)	44 (55.7)	46 (60.5)
Cardioversions per patient, range	0-10	0-3
EHRA score,[c] No. (%)		
II, mild symptoms	16 (20.3)	21 (27.6)
III, severe symptoms	47 (59.5)	40 (52.6)
IV, disabling symptoms	16 (20.3)	15 (19.7)
Left atrial diameter, mean (SD), mm	41.7 (6.4)	41.7 (4.9)
Left ventricular ejection fraction, mean (SD), %	56.2 (7.2)	56.1 (7.7)
Any of listed comorbidities, No. (%)	48 (60.8)	32 (42.1)
Hypertension	37 (46.8)	23 (30.3)
Chronic lung disease	6 (7.6)	2 (2.6)
Bradycardia or sick sinus syndrome	6 (7.6)	7 (9.2)
Sleep apnea	4 (5.1)	1 (1.3)
Stroke, transient ischemic attack, peripheral emboli	4 (5.1)	0
Diabetes	3 (3.8)	3 (3.9)
Heart failure	2 (2.5)	3 (3.9)
Coronary disease	2 (2.5)	3 (3.9)
Valvular disease	1 (1.3)	1 (1.3)
Pacemaker, No. (%)	3 (3.8)	2 (2.6)
Blood pressure, mean (SD), mm Hg		
Systolic	131 (17)	127 (16)
Diastolic	81 (11)	79 (10)
CHA_2DS_2-VASc score ≥2, No. (%)[d]	27 (34.2)	18 (23.7)
Score, median (IQR)	1 (0-2)	1 (0-1)
AF medication, No. (%)		
Oral anticoagulation	54 (68.4)	42 (55.3)
Medication VW class I or III	30 (38.0)	34 (44.7)
β-Blocker only	47 (59.5)	39 (51.3)

AF, atrial fibrillation; CHA_2DS_2-VASc, congestive heart failure, hypertension, age, diabetes, and stroke/transient ischemic attack–vascular disease; EHRA, European Heart Rhythm Association; IQR, interquartile range; VW, Vaughan-Williams classification of antiarrhythmic drugs.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Atrial fibrillation burden measured by an implantable cardiac monitor.

[c] The score assesses the severity of symptoms attributable to atrial fibrillation; class I, no symptoms and classes II, III, and IV indicate mild, severe, and disabling symptoms, with normal daily activity unaffected, affected, and discontinued, respectively.

[d] The CHA_2DS_2-VASc score estimates risk of ischemic stroke in patients with atrial fibrillation; score range, 0 to 9. Higher scores indicate higher risk for stroke; a score of 2 or higher denotes an indication for anticoagulation therapy.

3 years), patient event report for arrhythmia symptoms, and a 12-lead ECG were obtained at each visit. Quality-of-life and symptom questionnaires, 24-hour Holter recording, exercise test, blood tests, and echocardiographic examinations were performed at baseline, at 6 and 12 months, and annually thereafter. All comparisons were made between baseline (run-in) and 12-month follow-up or the last observation.

Statistical Analysis

In accordance with a slower-than-projected accrual of study patients despite attempts to improve recruitments and indications from 2 studies that the expected difference in primary end point (General Health score) was larger than originally anticipated,[6,9] the steering committee decided to recalculate the original sample size (270 patients) after careful consideration of potential alternatives, including a further prolongation of the study period. The new sample size calculation, based on these 2 publications,[6,9] assumed that the minimal detectable difference in the primary end point (General Health score) between the treatment groups was greater than or equal to 10.5 units (corresponding to 15% improvement, assuming a mean General Health score of 70 in the medication group). The originally anticipated difference was 7 (corresponding to an improvement of 10%).

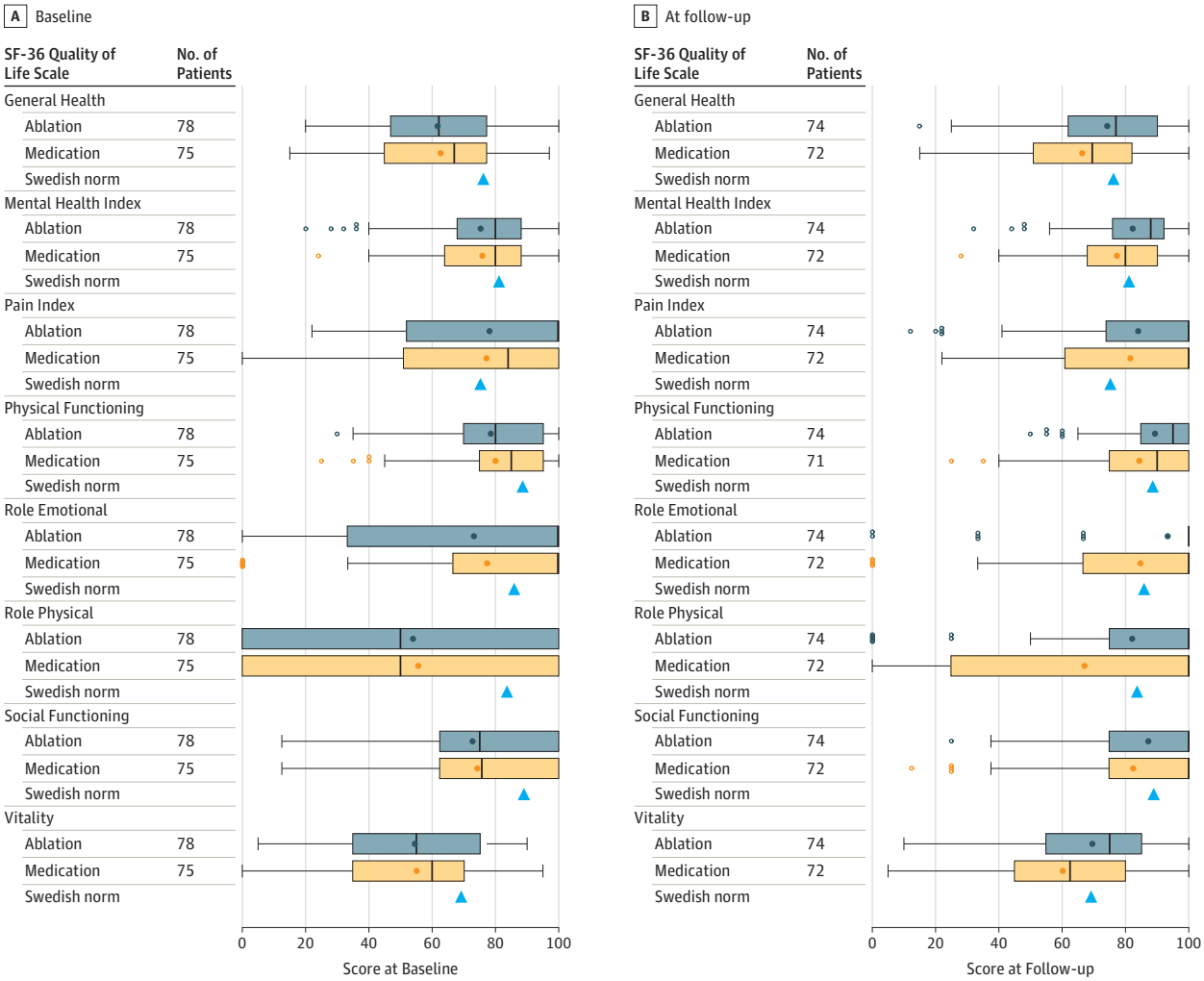
A sample size of approximately 116 patients in total was required for a power of 80% and a type I error rate of 5% (2-sided alternative). Forty patients were added to ensure the calculated number of patients for analysis at 12 months, allowing dropouts during the 4-year follow-up. In accordance with historical data,[13,14] we assumed that the variable was normally distributed and that the standard deviation for the change in General Health score was approximately 20 units.

Baseline data are given as the mean with standard deviations for continuous variables and percentages for categorical variables. The mean difference between treatment groups is presented with 95% CIs. The primary end point, SF-36 General Health score at 12 months, was analyzed using a *t* test and the method of last observation carried forward for observations with (partially) missing data, according to the prespecified primary analysis approach. All randomized patients were included in the intention-to-treat analysis.

Secondary continuous variables, including atrial fibrillation burden, were also analyzed with analysis of covariance, with the corresponding baseline values as covariates. Time to event data were analyzed with Kaplan-Meier graphs and log-rank tests with hazard ratios (HRs). A post hoc sensitivity analysis evaluated the General Health subscale and the other SF-36 subscales applying multiple imputation for missing values in a mixed-effect repeated-measure model with fixed effects for treatment group, visit (baseline, 6 months, and 12 months) and visit × treatment group, random patient (within site) effect, and site as repeated effect.

A post hoc explorative analysis of covariance was used to assess the relationship between improvements in General Health score and reduction in atrial fibrillation burden, including the effect of randomized treatment and number of antiarrhythmic drugs tested during follow-up. A 2-sided $P < .05$ defined statistical significance. No adjustments for multiple

Figure 2. Primary and Secondary End Points: Quality-of-Life Scores by Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)



Quality-of-life scores by the SF-36 survey in patients allocated to catheter ablation vs antiarrhythmic medication, with the Swedish general population as reference. The left and right edges of the boxes indicate the interquartile range (IQR). The dot inside indicates the mean value. The line inside the box indicates the median value. The whiskers extend from each box to the farthest point that remains within the end of the box ± 1.5 × IQR. Outliers are observations that are more extreme than ± 1.5 × IQR and marked by small circles.

A, At baseline the scores in the treatment groups were comparable and lower than in the Swedish normal population. Swedish norms originate from the SF-36 instruction manual.[15]

B, At 12-month follow-up, the ablation group improved significantly more than the medication group in all subscales except Bodily Pain and Social Functioning and reached the same score levels as the Swedish normal population. The Role Emotional result in the 12-month plot for the ablation group is explained by the fact that 89% of patients had a score of 100, so that quartiles 1 through 3 were all 100.

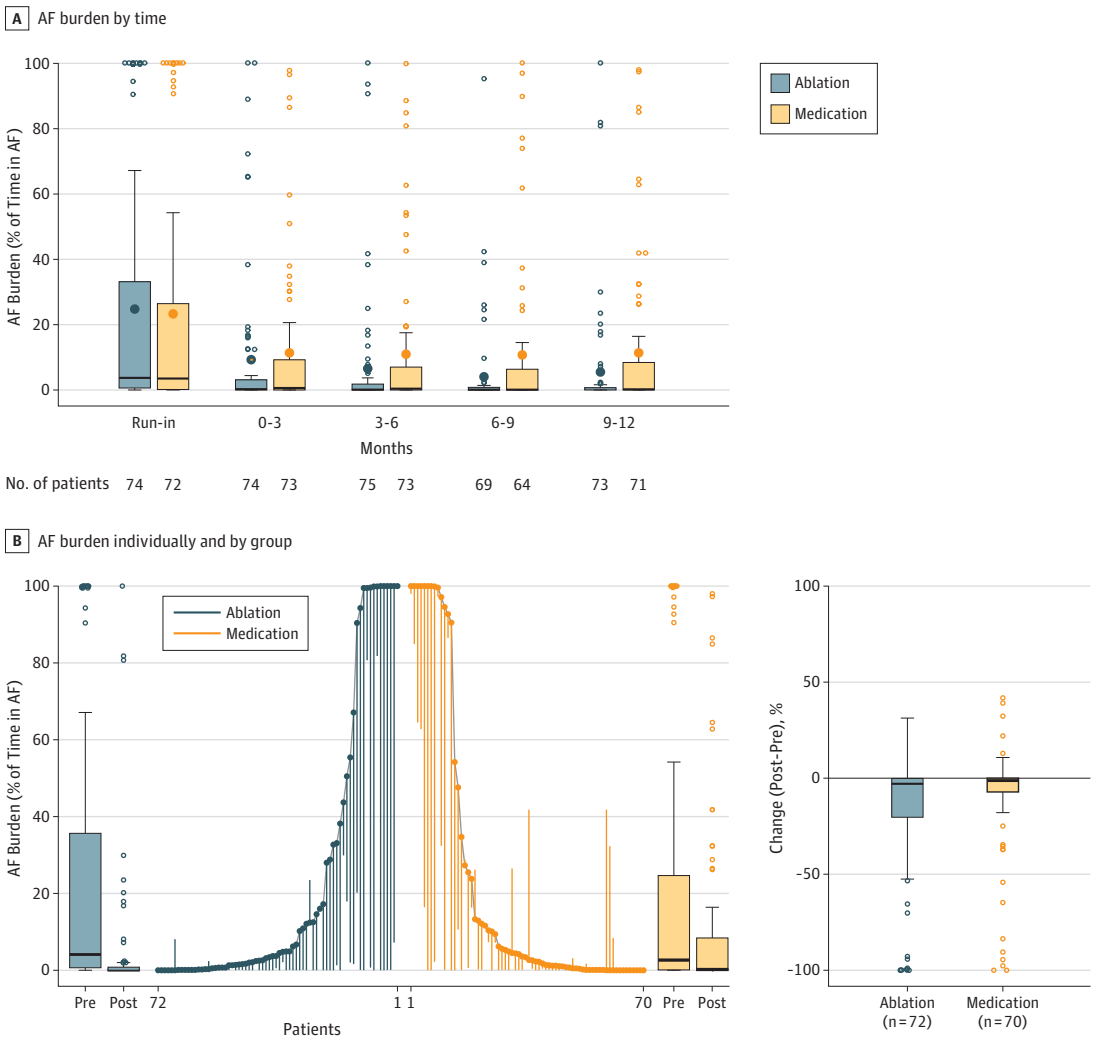
comparisons were undertaken and *P* values should not be used to infer definitive treatment effects for secondary outcomes; therefore, all findings from analyses of secondary end points and post hoc analyses should be considered exploratory. Data were managed by Viedoc database software, version 3.27. Analyses were conducted with SAS, version 9.4.

Results

Patients

Among the 155 patients included, 79 were randomized to receive catheter ablation and 76 to receive antiarrhythmic medication (Figure 1). Baseline characteristics are shown in **Table 1**. Of the 75 patients (94.9%) who underwent ablation, 60 underwent irrigated radiofrequency ablation and 15 underwent cryoballoon ablation. The pulmonary veins were completely isolated in 70 patients (93.3%) and a roof line was added in 1 patient (1.3%). Repeat ablation was performed in 14 patients (18.7%), who underwent a mean of 2.14 ablation procedures (SD, 0.36). Two patients (2.7%) crossed over to antiarrhythmic medication. The 74 patients (97.4%) starting antiarrhythmic medication received a mean of 1.71 agents (SD, 1.04; range, 1-5), most commonly flecainide, used in 52 patients (70.3%). The first drug used failed in 43 patients (58.1%). Eight patients (10.8%) crossed over to catheter ablation.

Figure 3. Secondary End Point Atrial Fibrillation Burden From the Implantable Cardiac Monitor



A, The box plot shows atrial fibrillation burden during run-in and at 4 points during follow-up in patients allocated to catheter ablation vs antiarrhythmic medication, with median values (horizontal line inside the box) and interquartile range (IQR, depicted by the bottom and top edges of the box). Whiskers that extend from each box indicate the range of values that are outside of the IQR but not far enough to be considered outliers. Outliers are observations that are more extreme than ± 1.5 × IQR and are marked by circles. The large dot indicates the mean value.

B, Atrial fibrillation burden displayed individually in both treatment groups. The parallel line plot is sorted by treatment group and prevalues (percentage of time) and then, within equal prevalues, postvalues. Pre- and postvalues of each patient on a common axis are shown, with difference depicted by the length of the line that runs between them. The boxes and whiskers are defined as in panel A. AF indicates atrial fibrillation; pre, run-in; and post, month 12.

Primary End Point and Overall Quality of Life

The primary end point, SF-36 General Health score, improved significantly more in the ablation group than in the medication group from baseline to 12 months (mean baseline score, 61.8 vs 62.7 [mean change, 11.9 vs 3.1]), with a mean treatment difference of 8.9 points (95% CI, 3.1-14.7; P = .003).

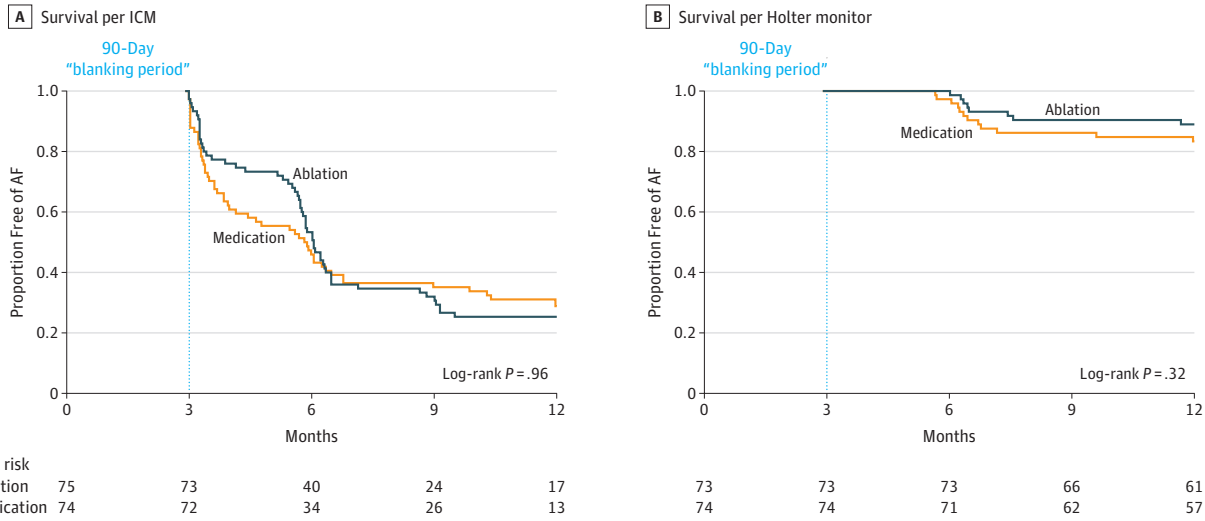
Of the remaining 7 SF-36 subscales, 5 were improved significantly by both treatments but significantly more in the ablation group than in the medication group. Bodily Pain and Social Functioning subscales showed no significant improvement (**Figure 2**, eTable 2 in Supplement 2), confirmed by post hoc sensitivity analyses (eTable 2 B-C in Supplement 2).

Secondary Explorative End Points

European Heart Rhythm Association symptom score improved significantly more in the ablation group (mean [SD], 3.0 [0.6] to 1.6 [0.8]) than in the medication group (2.9 [0.7] to 2.1 [1.1]) (mean treatment difference, −0.5 [95% CI, −0.9 to −0.2]; P = .003).

Atrial fibrillation burden recorded by the implantable cardiac monitor decreased significantly in both the ablation group (mean [SD], 24.9% [37.0%] to 5.5% [18.1%]; P < .001)

Figure 4. Secondary End Point Event-Free Survival From Atrial Fibrillation



No. at risk

Ablation	75	73	40	24	17
Medication	74	72	34	26	13
Ablation	73	73	73	66	61
Medication	74	74	71	62	57

Kaplan-Meier curves comparing survival free from atrial fibrillation episodes according to implantable cardiac monitor (A) and cumulative 24-hour Holter recordings in the 2 treatment groups (B). There were no significant differences between treatment groups. Events were not counted during the first 90-day blanking period (a period of therapeutic stabilization after ablation during which any occurrence of atrial fibrillation is not considered treatment failure or atrial fibrillation recurrence). For the implantable cardiac monitor, the median (quartile 1-3) observation time was 12.2 months (12.0-12.5 months) for the ablation group and 12.1 months (11.9-12.6 months) for the drug group. The 24-hour Holter recordings were obtained for 12.0 months (12.0-12.0 months) in the ablation group and 12.0 months (12.0-12.0) in the antiarrhythmic medication group.

and the medication group (23.3% [36.9%] to 11.5% [24.3%]; P = .002) (**Figure 3**A), displayed individually for both treatment groups in Figure 3B. The difference in least-square means for the change of atrial fibrillation burden from run-in to the first point (0-3 months) and second point (3-6 months) after the start of therapy was not statistically significant between treatment groups: −2.4 (95% CI, −8.7 to 3.9; P = .46) and −4.9 (95% CI, −11.1 to 1.3; P = .12), respectively. The mean reduction in atrial fibrillation burden was, however, significantly greater in the ablation than in the medication group from run-in to the third (6-9 months) and last point (9-12 months), with differences in least-square mean of −7.1 (95% CI, −13.2 to −1.0; P = .02) and −6.8 (95% CI, −12.9 to −0.7; P = .03), respectively, according to the ancillary analysis of covariance (Figure 3A).

Freedom from atrial fibrillation episodes on the implantable monitor during 12-month follow-up did not differ significantly between the ablation and the medication group (19/75 [25.3%] vs 22/74 [29.7%]; HR, 0.99 [95% CI, 0.68-1.44]; P = .96) (**Figure 4**A). The corresponding analysis on cumulative 24-hour Holter recording showed no significant difference in freedom from episodes between ablation and medication (62/73 [84.9%] vs 58/74 [78.4%]; HR, 0.64 [95% CI, 0.26-1.55]; P = .27). The atrial fibrillation recurrence rate was markedly higher when measured with the implantable cardiac monitor than with Holter recordings (Figure 4B).

The mean (SD) number of cardioversions after the 90-day blanking period at 12-month follow-up did not differ significantly between the ablation and the medication group: 0.39 (1.10) vs 0.59 (1.40) (mean difference [95% CI], −0.21 [−0.62 to 0.20], P = .32).

Post Hoc End Points and Analyses

Freedom from a composite of first clinical outcome events was significantly higher in the ablation group than in the medication group at 12-month follow-up: 47/75 (62.7%) vs 30/74 (40.5%) (HR, 0.50 [95% CI, 0.31-0.81]; P = .004) (eFigure in Supplement 2).

The improvement in SF-36 General Health score at 12 months vs baseline was inversely related to the reduction in atrial fibrillation burden on the implantable monitor, whereas the effects of randomized treatment and number of antiarrhythmic drugs tested disappeared during follow-up (eTable 3 in Supplement 2).

Serious Adverse Events

The most common adverse events were urosepsis (5.1%) in the ablation group and atrial tachycardia (3.9%) in the medication group, managed uneventfully (**Table 2**).

Discussion

This multicenter randomized trial demonstrated that among patients with atrial fibrillation whose condition did not respond to either a β-blocker or an antiarrhythmic drug, pulmonary vein isolation resulted in a significantly greater improvement in SF-36 General Health score, the primary end point, compared with optimized antiarrhythmic medication. The magnitude of the improvement in General Health score of 11.9 points in the ablation group (3.1 in the medication group), with an 8.9-point treatment difference, suggested that the between-group difference was clinically relevant, as indicated by the US SF-36 manual, which states

Table 2. Serious Adverse Events by Randomized Treatment

Events	No. (%)	
	Ablation (n = 79)	Medication (n = 76)
Procedural or drug-initiation-related complications[a]		
Urinary tract infection, urosepsis	4 (5.1)	0
Groin complications (major groin bleeding, hematoma, knot on ablation catheter when withdrawn in groin sheet causing vagal reaction)	3 (3.8)	0
Tamponade or pericardial effusion	2 (2.5)	0
Transient ischemic attack	1 (1.3)	0
Nonarrhythmic drug related (fever, emesis, dizziness, atrial flutter)	0	5 (6.6)
AV block II, bradycardia, sinus arrests	0	2 (2.6)
Ventricular tachycardia	0	2 (2.6)
Total	10 (12.7)	9 (11.8)
Cardiovascular complications during follow-up		
Presyncope, sinus arrests, or pacemaker[b]	1 (1.3)	2 (2.6)
Stroke, transient ischemic attack, left atrial appendage thrombus	1 (1.3)	2 (2.6)
Ventricular tachycardia	1 (1.3)	0
Pulmonary embolism, myocardial infarction	1 (1.3)	1 (1.3)
Pocket infection of implantable cardiac monitor	0	1 (1.3)
Tricuspid isthmus ablation or atrial tachycardia ablation	0	3 (3.9)
Total	4 (5.1)	9 (11.8)
Sum of total complications	14 (17.7)	18 (23.7)

[a] All antiarrhythmic drug-related events led to withdrawal of the drug; the bradycardias and ventricular tachycardias resolved. Procedure-related infections, the most common safety event, were all related to urinary catheters during the ablation procedure. Other serious adverse events were mainly known adverse effects of drugs requiring withdrawals of antiarrhythmic drugs. There were no deaths related to atrioesophageal fistulae, pulmonary vein stenosis, or procedures.

[b] Pacemakers were implanted in 1 patient in each treatment group because of sick sinus syndrome. The tamponade was managed by pericardiocentesis.

that a 5-point change corresponds to a socially and clinically significant difference, whereas 10 points translates to a moderate difference and 20 points to a large one.[12]

Both treatments improved quality of life and European Heart Rhythm Association symptom score, which was expected because a majority of the patients had been treated with β-blockers only, rendering them comparable to cohorts in trials evaluating ablation as a first-line therapy.[7,9,11] A limitation in most trials has been the inclusion of patients who already failed at least 1 antiarrhythmic drug, which inevitably has resulted in bias favoring catheter ablation.[6,10,16]

In this trial, nearly all SF-36 subscale scores and the European Heart Rhythm Association symptom score improved significantly more after ablation compared with antiarrhythmic medication, findings reinforcing the perception that catheter ablation should be offered as a first-line treatment in a population who failed a β-blocking agent only,[9,17] as well as supporting guidelines on atrial fibrillation ablation.[2]

The SF-36 questionnaire has been criticized for being less sensitive in atrial fibrillation populations compared with disease-specific questionnaires, such as the AF6.[18] However, in previous ablation trials, arrhythmia-specific questionnaires[17] and the EQ-5D tool[7] failed to detect differences in quality of life. Furthermore, the AF6 was limited to cardioversion trials without proper controls.[18,19] These observations and the association between General Health score and atrial fibrillation burden shown in this study argue in favor of the well-validated SF-36 questionnaire. A change in the perception of atrial fibrillation episodes, as reported earlier,[20,21] may also explain an improved quality of life.

Although the exploratory nature of atrial fibrillation burden is a limitation, the observation that it decreased significantly in both treatment groups was expected because the majority of the patients had used only β-blocking agents. Similar findings were reported in a trial evaluating catheter ablation as the first-line treatment for symptomatic paroxysmal atrial fibrillation.[11] In contrast, this study could demonstrate by using an implantable cardiac rhythm monitor that the true atrial fibrillation burden decreased significantly more by ablation than by medication during follow-up, a difference that their extensive 7-day Holter monitoring failed to detect.[11] Apart from better rhythm monitoring, these divergent findings may also be related to the lower (10.8%) crossover rate from antiarrhythmic medication to ablation in this study compared with previous experience (36%).[11] Moreover, the post hoc analysis finding that the greater improvement in General Health score was inversely related to the greater reduction in atrial fibrillation burden by ablation, whereas the effect of randomized treatment disappeared, favored a true treatment effect by ablation.

To our knowledge, no other randomized trial comparing these 2 treatment strategies has used symptoms or quality of life, a variable that directly reflects the indication for treatment, as a primary end point.[7,9,11] In previous randomized atrial fibrillation ablation trials, the primary efficacy end point was either the standard[2] 30-second atrial fibrillation episode[5-10,22] or substitutes of atrial fibrillation burden.[3,4,11,16] The limitations with such interrupted arrhythmia monitoring[23-26] and the effects of inhomogeneous distribution of episodes on long-term follow-up[27,28] have been reported elsewhere, as has the 98.5% high accuracy of the implantable monitor in detecting atrial fibrillation.[29]

The almost 7-fold underestimation of atrial fibrillation recurrence rate by the 24-hour Holter monitor has not previously been described in randomized trials, to our knowledge, indicating that atrial fibrillation burden may be underestimated unless an implantable cardiac monitor is used.

The major complications related to ablation seemed comparable to those reported earlier,[11,30,31] except for procedure-related urosepsis.

Limitations

This study has several limitations. First, the study assessments were not blinded. Because this trial did not include a sham procedure, one cannot rule out that differences in symptoms and quality of life were attributed to bias, a procedure-related placebo effect. Second, because of the rapid

development of catheter ablation technologies and their improvement, had the catheter ablations been performed today, they might have resulted in even better outcomes for patients allocated to ablation. Third, there is the potential for type I error related to multiple secondary end points in the absence of a prespecified statistical approach to deal with them. All secondary end points were therefore regarded as exploratory. Fourth, these results may not be generalizable to centers with less favorable outcomes of catheter ablation.

Conclusions

Among patients with symptomatic atrial fibrillation despite use of β-blockers or antiarrhythmic medication, the improvement in quality of life at 12 months was greater for those treated with catheter ablation compared with antiarrhythmic medication. Although the study was limited by absence of blinding, catheter ablation may offer an advantage for quality of life.

ARTICLE INFORMATION

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