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Radiofrequency Ablation as Initial Therapy in Paroxysmal Atrial Fibrillation

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ABSTRACT

BACKGROUND

There are limited data comparing radiofrequency catheter ablation with antiarrhythmic drug therapy as first-line treatment in patients with paroxysmal atrial fibrillation.

METHODS

We randomly assigned 294 patients with paroxysmal atrial fibrillation and no history of antiarrhythmic drug use to an initial treatment strategy of either radiofrequency catheter ablation (146 patients) or therapy with class IC or class III antiarrhythmic agents (148 patients). Follow-up included 7-day Holter-monitor recording at 3, 6, 12, 18, and 24 months. Primary end points were the cumulative and per-visit burden of atrial fibrillation (i.e., percentage of time in atrial fibrillation on Holter-monitor recordings). Analyses were performed on an intention-to-treat basis.

RESULTS

There was no significant difference between the ablation and drug-therapy groups in the cumulative burden of atrial fibrillation (90th percentile of arrhythmia burden, 13% and 19%, respectively; P=0.10) or the burden at 3, 6, 12, or 18 months. At 24 months, the burden of atrial fibrillation was significantly lower in the ablation group than in the drug-therapy group (90th percentile, 9% vs. 18%; P=0.007), and more patients in the ablation group were free from any atrial fibrillation (85% vs. 71%, P=0.004) and from symptomatic atrial fibrillation (93% vs. 84%, P=0.01). One death in the ablation group was due to a procedure-related stroke; there were three cases of cardiac tamponade in the ablation group. In the drug-therapy group, 54 patients (36%) underwent supplementary ablation.

CONCLUSIONS

In comparing radiofrequency ablation with antiarrhythmic drug therapy as first-line treatment in patients with paroxysmal atrial fibrillation, we found no significant difference between the treatment groups in the cumulative burden of atrial fibrillation over a period of 2 years. (Funded by the Danish Heart Foundation and others; MANTRA-PAF ClinicalTrials.gov number, NCT00133211.)

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Radiofrequency catheter ablation has emerged as an effective therapy for patients with paroxysmal atrial fibrillation who have recurrent episodes of arrhythmia despite antiarrhythmic drug therapy.[1-8] It has been suggested that pulmonary-vein isolation can also be used as first-line treatment in selected patients with paroxysmal atrial fibrillation,[6] and there are physiological reasons to assume that ablation as first-line therapy might be more effective than later intervention. Irreversible structural changes such as fibrosis and myolysis are commonly detected in the atria when atrial fibrillation has become persistent,[9,10] and extensive atrial fibrosis detected by magnetic resonance imaging predicts a poor outcome after ablation therapy.[11,12] In contrast, excellent results of pulmonary-vein isolation have been reported in young patients with atrial fibrillation and no concomitant heart disease.[13,14] However, only one small, single-center trial with short-term follow-up has compared catheter ablation with antiarrhythmic drug treatment as first-line therapy.[15] The aim of the present trial was to compare the long-term efficacy of an initial strategy of radiofrequency catheter ablation with an initial strategy of antiarrhythmic drug therapy in a larger population of patients with paroxysmal atrial fibrillation.

Methods

Study Design

The Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation (MANTRA-PAF) trial[16] was a multicenter, randomized trial that was sponsored by the Danish Heart Foundation and Biosense Webster. The steering committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org) designed the trial, gathered and analyzed the data, and made the decision to submit the manuscript for publication. The first author drafted the manuscript, and all authors contributed to its revision. The sponsors had no influence on the content of the manuscript. The authors take responsibility for the completeness and accuracy of the data and analysis and for the fidelity of this report to the trial protocol, which is available at NEJM.org.

The trial was conducted in accordance with the Declaration of Helsinki and was approved by regional ethics committees and the Danish Data Protection Agency. Adverse events were reported annually to the ethics committees. All patients gave written informed consent before enrollment.

Patient Selection and Randomization

Patients with symptomatic paroxysmal atrial fibrillation who were considered to be appropriate candidates for rhythm-control therapy were screened. Inclusion criteria were at least two episodes of symptomatic atrial fibrillation within the preceding 6 months but no episode of atrial fibrillation that was longer than 7 days (without spontaneous termination or cardioversion). The exclusion criteria were an age of more than 70 years, previous or ongoing treatment with class IC or class III antiarrhythmic drugs, contraindication to both class IC and class III agents, previous ablation for atrial fibrillation, a left atrial diameter of more than 50 mm, a left ventricular ejection fraction of less than 40%, contraindication to oral anticoagulation therapy, moderate-to-severe mitral valve disease, severe heart failure (New York Heart Association functional class III to IV at the time of enrollment), expected surgery for structural heart disease, and secondary atrial fibrillation (due to cardiac surgery, infection, or hyperthyroidism).

The patients were randomly assigned to an initial strategy of either radiofrequency catheter ablation or treatment with a class IC or class III antiarrhythmic drug. Block randomization was performed with the use of an automated telephone randomization system, after stratification according to center, sex, and hypertension status. Each included patient underwent a baseline 7-day Holter-monitor recording.

Radiofrequency Catheter Ablation

Oral anticoagulation with a stable international normalized ratio of 2.0 or higher was ensured for at least 3 weeks before ablation. Transesophageal echocardiography was performed within 24 hours before the procedure to rule out the presence of left atrial thrombi. After transseptal puncture of the interatrial septum, intravenous heparin was administered according to institutional standards. The ablation procedure was guided by electroanatomical mapping (CARTO, Biosense Webster).

Percutaneous transvenous radiofrequency catheter ablation was performed by encircling the left- and right-sided pulmonary veins with either a 3.5-mm catheter with an irrigated tip (NaviStar ThermoCool, Biosense Webster) or an 8-mm solid-

tip catheter (for 15 procedures; NaviStar DS, Biosense Webster). The irrigated catheter (saline flow, 17 ml per minute) had a maximum power setting of 40 W, and the solid-tip catheter had a maximum power setting of 80 W; both had a target temperature of 55°C. Reduced power was used in the left atrial posterior wall to avoid excessive heating of the esophagus and other adjacent structures. The goal of ablation was the elimination of all high-frequency electrical activity with an amplitude exceeding 0.2 mV inside the encircled areas, which was documented by electroanatomical mapping or by the use of circular multipolar catheters (which were used for 138 procedures) at the operator's discretion. Additional ablation sites inside the encircled areas but outside the pulmonary veins were allowed in order to achieve the ablation goal. A supplementary linear ablation was placed along the roof of the left atrium between the two encircled areas. Ablation lines in the mitral and tricuspid isthmuses were optional.

Antiarrhythmic medication was allowed during the initial 3 months after the ablation (the postablation "blanking period"). Thereafter, supplementary antiarrhythmic drug therapy was discouraged. Patients with recurrent atrial fibrillation after the blanking period were offered a second ablation procedure.

ANTIARRHYTHMIC DRUG THERAPY

The first-line medication was a class IC agent (either flecainide at a dose of 200 mg per day or propafenone at a dose of 600 mg per day). If class IC agents were contraindicated, a class III agent (either amiodarone at a dose of 200 mg per day or sotalol at a dose of 160 mg per day) was used. During treatment with class IC agents, supplementary use of a beta-blocker, a calcium-channel blocker, or digoxin was recommended. Combinations of class IC and class III agents were not allowed. An aggressive rhythm-control strategy, with the use of direct-current cardioversion and trial of all clinically appropriate antiarrhythmic drugs, was recommended for any patient with recurrent atrial fibrillation. If antiarrhythmic drug therapy failed, supplementary ablation of atrial fibrillation was offered as clinically indicated.

FOLLOW-UP

Clinical follow-up and a 7-day Holter-monitor recording were scheduled at 3, 6, 12, 18, and 24 months. All the Holter recordings were analyzed at Aarhus University Hospital by the same experienced technician; Holter analysis was blinded with respect to randomization and treatment.[16] Patients were also instructed to contact the study center if they had palpitations or other symptoms between the follow-up visits. Patients were given a logbook to record information on arrhythmia symptoms and contacts with other health care providers.[17]

STUDY OUTCOMES

The primary study end points were the burden of atrial fibrillation (defined as the percentage of time in atrial fibrillation on each Holter recording) and the cumulative burden of atrial fibrillation (defined as the percentage of time in atrial fibrillation on all the Holter recordings obtained during follow-up). Only episodes of atrial fibrillation longer than 1 minute were included in the analysis. Secondary outcome measures included freedom from any atrial fibrillation and freedom from symptomatic atrial fibrillation at 24 months of follow-up, cumulative and per-visit burden of symptomatic atrial fibrillation, time to first recurrence of atrial fibrillation after the blanking period, and atrial flutter longer than 1 minute. Quality of life was assessed at baseline and at 12 and 24 months with the use of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) physical-component summary score and mental-component summary score (both of which range from 0 to 100, with higher scores indicating greater well-being). Serious adverse events were recorded as described previously.[16]

STATISTICAL ANALYSIS

Characteristics of the burden of atrial fibrillation, as defined for the MANTRA-PAF trial, in patients with paroxysmal atrial fibrillation were unknown when the trial was planned. Power calculations were therefore based on an assumption of freedom from atrial fibrillation after 24 months in 75% of the patients in the ablation group versus 60% of the patients in the drug-therapy group. Detection of such a difference between the two treatment groups at a power of 80% and a two-sided alpha level of 0.05 required an enrollment of 150 patients per group.

Treatment groups were compared on an intention-to-treat basis. Before the analysis, missing Holter data were replaced with data from a proxi-

Table 1. Baseline Characteristics of the Patients According to Assignment to Initial Treatment with Radiofrequency Ablation or Antiarrhythmic Drugs.*

Characteristic	Ablation (N=146)	Drug Therapy (N=148)
Age — yr	56±9	54±10
Male sex — no. (%)	100 (68)	106 (72)
Blood pressure — mm Hg		
Systolic	138±19	135±17
Diastolic	82±9	82±10
Body-mass index†	27±4	27±4
Medical history — no. (%)		
Coronary artery disease	6 (4)	2 (1)
Hypertension	43 (29)	53 (36)
Valvular disease	7 (5)	15 (10)
Previous valvular intervention	1 (1)	1 (1)
Previous stroke or TIA	6 (4)	5 (3)
Pacemaker	5 (3)	6 (4)
Thyroid disease	10 (7)	10 (7)
Diabetes mellitus	6 (4)	10 (7)
Chronic lung disease	8 (5)	6 (4)
Left atrial size, parasternal long axis — mm	40±6	40±5
Left ventricular ejection fraction — no.‡		
>60%	116	121
40–60%	29	26
New York Heart Association functional class — no.		
I	131	128
II	15	19
III	0	1
$CHADS_2$ score — no.§		
0	92	80
1	37	49
2	13	14
3	3	4
4	1	1

* Plus–minus values are means ±SD. There were no significant differences (at $P<0.05$) between the two groups. TIA denotes transient ischemic attack.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Echocardiographic data were missing for one patient in each group.
§ The $CHADS_2$ score is a measure of the risk of stroke in patients with atrial fibrillation, with scores ranging from 0 to 6 and higher scores indicating a greater risk. Congestive heart failure, hypertension, an age of 75 years or older, and diabetes mellitus are each assigned 1 point, and previous stroke or TIA is assigned 2 points; the score is calculated by summing all the points for a given patient.

mate examination according to a prespecified imputation algorithm.[16] Baseline characteristics were compared with the use of Pearson's chi-square test and the Mann–Whitney test. Analysis of the burden of atrial fibrillation was performed with the use of the Mann–Whitney test, the Kruskal–Wallis test, and the Wilcoxon signed-rank test. Freedom from atrial fibrillation and other categorical variables were compared with the use of Pearson's chi-square test. Time to recurrence of atrial fibrillation was compared by means of a univariate Cox regression analysis. Quality of life was analyzed by means of a repeated-measures analysis of variance.

Data were managed with the use of SIR/DBMS and SIR/FORMS database software (SIR). Statistical analysis was performed with the use of SPSS software, version 19 (IBM); BMDP software, release 8.1 (Statistical Solutions); and Stata software, version 11 (StataCorp). A two-sided P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

PATIENTS

From June 2005 through March 2009, a total of 294 patients were enrolled in the MANTRA-PAF trial and randomly assigned to an initial strategy of either radiofrequency catheter ablation (146 patients) or antiarrhythmic drug therapy (148 patients) (Fig. 1 in the Supplementary Appendix). The mean (±SD) age was 55±10 years, and 206 of the patients were men. Baseline characteristics were well balanced between the two groups (Table 1). Additional baseline characteristics, including particulars of previous episodes of atrial fibrillation and recent medications, are shown in Table 1 in the Supplementary Appendix.

In the ablation group, 140 patients (96%) underwent a mean of 1.6±0.7 procedures. Among patients who underwent repeat ablation, the total number of ablations was two in 58 patients, three in 8 patients, and four in 3 patients. Indications for repeat ablation were left atrial arrhythmias in 79 procedures (atrial fibrillation in 74 and left atrial flutter in 5). In the remaining 4 procedures, the indications were right atrial flutter (in 2 patients), atrioventricular nodal reentrant tachycardia (in 1 patient), and focal atrial tachycardia (in 1 patient). At 24 months, 13 patients in the ablation group were receiving antiarrhythmic drug therapy.

In the drug-therapy group, a total of 146 patients (99%) were treated with class IC antiarrhyth-

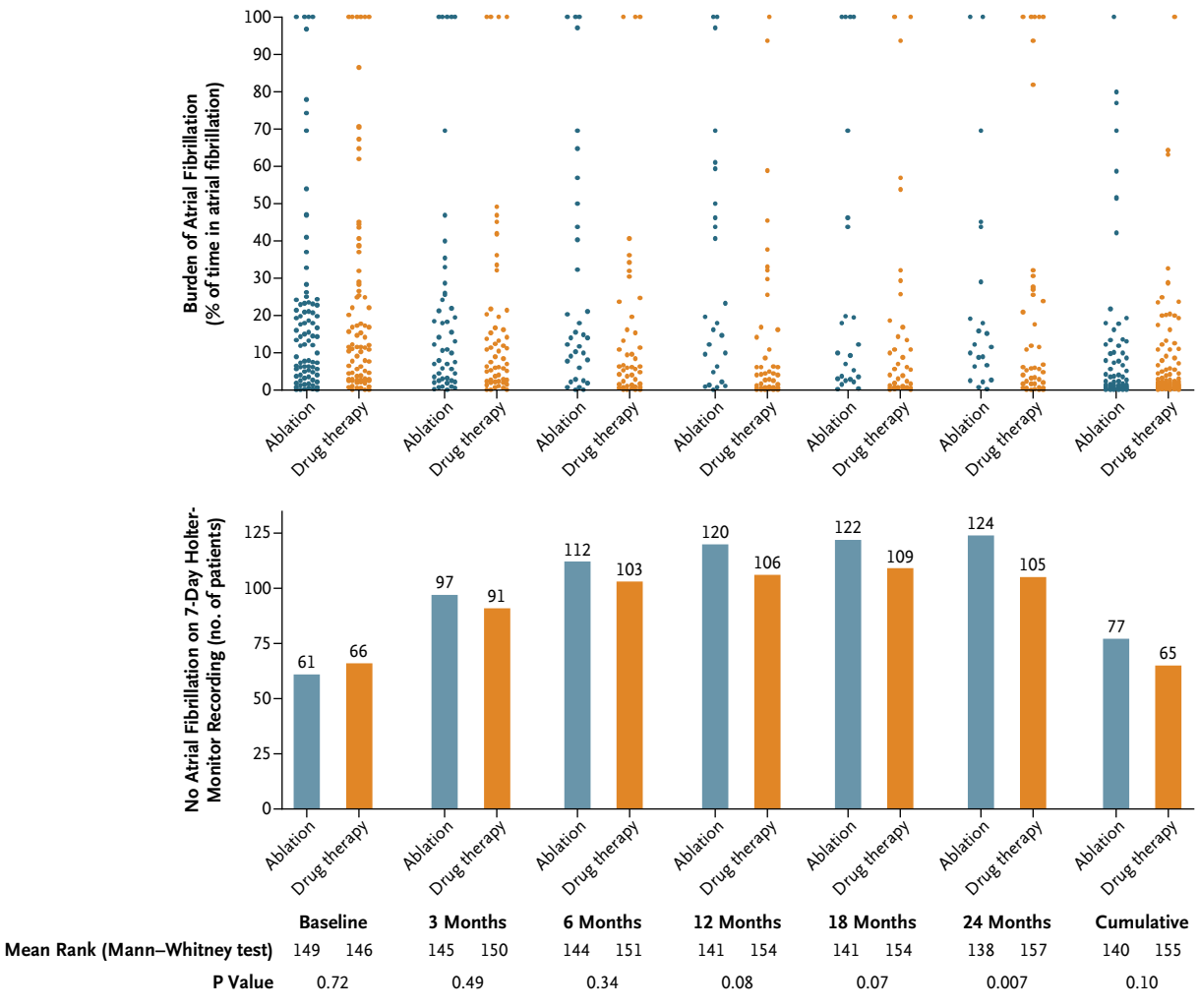

Figure 1. Burden of Atrial Fibrillation and Proportion of Patients Who Were Free of Atrial Fibrillation during the 2-Year Study Period, According to Treatment Group.

Shown are the burden of atrial fibrillation (upper graph) and the number of patients without atrial fibrillation (lower graph) in 7-day Holter-monitor recordings at baseline, at each follow-up visit, and cumulatively during follow-up. The mean rank (Mann–Whitney test) and P values for group comparisons of the burden of atrial fibrillation are shown at the bottom of the figure.

mic drugs (131 patients) or class III antiarrhythmic drugs (15 patients). The mean number of agents used during the study period was 1.26±0.46 (range, 1 to 3). Supplementary radiofrequency ablation was performed in 54 patients (36%), who underwent a mean of 1.6±0.7 ablation procedures, the first at a mean of 8.7±6.5 months after inclusion in the study. Ablation was performed for left atrial arrhythmias in 81 procedures (atrial fibrillation in 78 and left atrial flutter in 3). In 6 procedures, ablation was performed for right atrial flutter.

Treatment status after 24 months of follow-up is shown in Figure 1 in the Supplementary Appendix. Follow-up was completed in May 2011.

BURDEN OF ATRIAL FIBRILLATION

Holter recordings were available for analysis from 96% of the follow-up visits. The burden of atrial fibrillation was significantly lower at each follow-up visit than at baseline in both treatment groups ($P<0.001$ for all comparisons). There were no significant differences between the ablation and

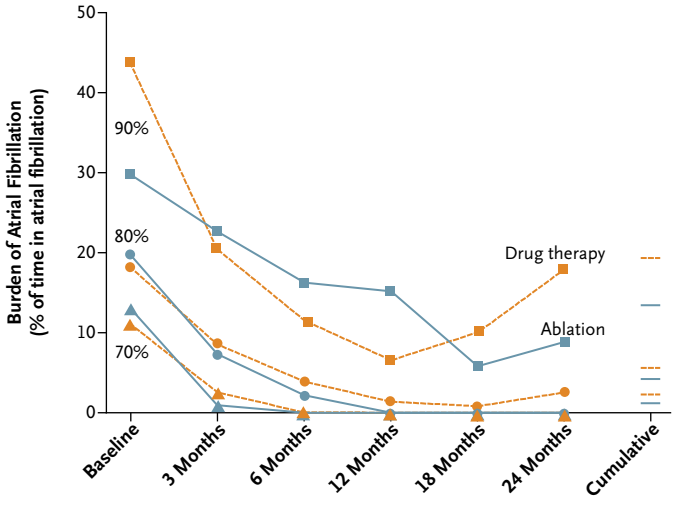

Figure 2. Percentile of Atrial-Fibrillation Burden According to Treatment Group.

Percentiles (70%, 80%, and 90%) of the burden of atrial fibrillation in the two groups at baseline and during follow-up are shown. The same percentiles are also shown for the cumulative burden of atrial fibrillation.

drug-therapy groups in the cumulative burden of atrial fibrillation (90th percentile of arrhythmia burden, 13% and 19%, respectively; P=0.10) or in the burden of atrial fibrillation at 3, 6, 12, or 18 months. The burden of atrial fibrillation was significantly lower in the ablation group than in the drug-therapy group at 24 months (90th percentile, 9% vs. 18%; P=0.007) (Fig. 1 and 2).

SECONDARY OUTCOMES

Significantly more patients in the ablation group than in the drug-therapy group were free from any atrial fibrillation (85% vs. 71%, P=0.004) and from symptomatic atrial fibrillation (93% vs. 84%, P=0.01) at 24 months. The results were confirmed when values for missing Holter data were not imputed (any atrial fibrillation, 88% vs. 74% [P=0.003]; symptomatic atrial fibrillation, 95% vs. 84% [P=0.006]). The cumulative burden of symptomatic atrial fibrillation did not differ significantly between the ablation and drug-therapy groups (P=0.12). At 24 months, the burden of symptomatic atrial fibrillation was lower in the ablation group than in the drug-therapy group (90th percentile, 0% vs. 3%; P=0.01). After the blanking period, there was no significant difference in time to first recurrence of atrial fibrillation between the groups (median time to recurrence, 25 days with ablation and 27 days with drug therapy; hazard ratio for ablation vs. drug therapy, 0.79; 95% confidence interval, 0.57 to 1.09; P=0.16).

Atrial flutter was detected in 31 patients in the ablation group and 40 patients in the drug-therapy group (P=0.25) during the 2-year follow-up period. Atrial flutter was more commonly observed in patients in the drug-therapy group who were treated with supplementary ablation than in those who were not (43% vs. 18%, P=0.002).

Quality of life did not differ significantly between the groups at baseline. The SF-36 physical-component and mental-component summary scores improved significantly from baseline in both treatment groups. The physical-component summary score improved more over time in the ablation group than in the drug-therapy group (Table 2).

ADVERSE EVENTS

The total number of serious adverse events did not differ significantly between the groups (Table 3). Twenty patients in the ablation group and 16 pa-

Table 2. SF-36 Quality-of-Life Scores.*

Summary Score	Baseline		12 Months		24 Months		P Value for Effect of Group	P Value for Effect of Time	P Value for Interaction
	Ablation	Drug Therapy	Ablation	Drug Therapy	Ablation	Drug Therapy			
Physical component	44.3±8.9	45.2±8.9	50.2±8.5	47.5±9.7	50.0±8.8	47.9±8.9	0.23	<0.001	0.01
Mental component	45.2±11.7	46.1±11.2	50.8±9.3	50.1±8.5	51.1±9.2	50.9±8.0	0.93	<0.001	0.39

* Plus–minus values are means ±SD. Both the physical-component and mental-component summary scores of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) range from 0 to 100, with higher scores indicating greater well-being. P values for the effect of group, time, and interaction between time and group are from a repeated-measures analysis of variance.

tients in the drug-therapy group had serious adverse events (P=0.45). Three patients in the ablation group had cardiac tamponade as a consequence of the ablation procedure. Three patients in the ablation group and four patients in the drug-therapy group died during the study. One death in the ablation group was caused by a procedure-related cerebral stroke. The other causes of death were not considered to be related to the treatment (Table 3).

Table 3. Serious Adverse Events.*

Event	Ablation	Drug Therapy
	no. of events	
Death	3†	4‡
Cancer	6	4
Atrial flutter with an atrioventricular conduction ratio of 1:1	0	2
Atrial flutter or atrial tachycardia	3	3
Perimyocarditis	1	0
Stroke	1	0
TIA	1	1
Tamponade	3	0
Pericardial effusion without the need for pericardial puncture	0	1
Suspected perforation at transseptal puncture, no pericardial effusion	1	0
Pulmonary-vein stenosis	1	0
Hospitalization for heart failure	0	2
Hematoma related to anticoagulation	1	0
Bradycardia with the need for a cardiac pacemaker	0	1
Ventricular tachycardia and implantation of an ICD	1	0
Retroperitoneal bleeding, coiling of small artery	1	0
Chest discomfort	1	0
Discomfort probably due to medication§	0	2
Rupture of the rotator cuff	0	1
Knee osteoarthritis requiring arthroscopy	1	0
Gallbladder surgery	0	1
Total	25	22

* Events reported as serious adverse events during the study are shown. Some patients had more than one serious adverse event. ICD denotes implantable cardioverter–defibrillator.
† The causes of death were stroke, prostate cancer, and sudden death, cause unknown.
‡ The causes of death were lung cancer (two patients), myocardial infarction (one patient), and sudden death, cause unknown (one patient).
§ One patient had weakness due to bradycardia, and another patient reported tiredness.

DISCUSSION

We compared radiofrequency ablation with antiarrhythmic drug therapy as first-line treatment in patients with paroxysmal atrial fibrillation. There was no significant difference between the two treatment strategies in the cumulative burden of atrial fibrillation over a period of 2 years. Given the risk of complications with ablation, our data support the current guidelines recommending antiarrhythmic drugs as first-line treatment in most patients with paroxysmal atrial fibrillation.[6-8]

However, some advantages of ablation were suggested by our data. After 24 months, the burden of atrial fibrillation was lower and more patients were free from atrial fibrillation in the ablation group than in the drug-therapy group, findings suggesting that the efficacy of catheter ablation may be more durable than that of currently available antiarrhythmic drugs. Although quality of life improved in both treatment groups, there was more improvement in physical well-being with ablation than with drug therapy during long-term follow-up (although, since our trial could not be blinded, this difference might be attributable in part to a placebo effect). Furthermore, 36% of patients initially assigned to antiarrhythmic drug therapy eventually underwent ablation for recurrent atrial fibrillation (most of them during the first year). This finding suggests that even though an initial strategy of drug treatment is appropriate, a substantial minority of patients so treated may eventually require ablation for adequate rhythm control.

We used 7-day Holter recordings to detect atrial fibrillation at baseline and during follow-up.[17] This method is more effective than shorter Holter recordings or symptom-guided electrocardiograms (ECGs).[18] More extensive ECG monitoring probably would have detected additional episodes of atrial fibrillation,[19] but many patients are reluctant to undergo longer recordings. According to recent research, leadless implantable cardiac monitors can detect episodes of atrial fibrillation accurately for much longer observation periods than long-term ECG recordings.[20] However, implantable devices were not available when this study was launched, and even these devices cannot detect very short episodes of atrial fibrillation.

A number of limitations of our trial should be noted. Elimination of high-frequency electrical activity with an amplitude exceeding 0.2 mV in-

side the encircled areas around the pulmonary veins was used as the end point of ablation. Because of the rapid development of ablation techniques, this is no longer considered the state-of-the-art approach. Today, there is agreement that the goal of ablation for atrial fibrillation should be complete electrical isolation of the pulmonary veins.[6,21] We cannot rule out the possibility that the results of ablation would have been better if we had documented the isolation of the pulmonary veins by using circular multipolar catheters in all patients.[22,23]

Our results are valid for relatively young, symptomatic patients with no major coexisting conditions but should not be extrapolated to elderly patients, to those with persistent or permanent atrial fibrillation, or to those with severe heart disease. Our study was performed in a group of centers that differed with respect to the volume of patients and degree of experience with ablation of atrial fibrillation. Thus, it is likely that our results are more representative of the broad general experience with ablation than those from a single high-volume center. The rate of complications from ablation in our trial was similar to rates reported previously.[24,25] One patient died from a procedure-related stroke, a finding that underscores the risk of lethal complications associated with left atrial ablation.

In conclusion, our study of radiofrequency ablation as compared with antiarrhythmic drug therapy as an initial strategy in patients with paroxysmal atrial fibrillation showed no significant difference between the two treatment strategies in the cumulative burden of atrial fibrillation over a period of 2 years.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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