The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 1, 2018 VOL. 378 NO. 5

Catheter Ablation for Atrial Fibrillation with Heart Failure

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ABSTRACT

BACKGROUND

Mortality and morbidity are higher among patients with atrial fibrillation and heart failure than among those with heart failure alone. Catheter ablation for atrial fibrillation has been proposed as a means of improving outcomes among patients with heart failure who are otherwise receiving appropriate treatment.

METHODS

We randomly assigned patients with symptomatic paroxysmal or persistent atrial fibrillation who did not have a response to antiarrhythmic drugs, had unacceptable side effects, or were unwilling to take these drugs to undergo either catheter ablation (179 patients) or medical therapy (rate or rhythm control) (184 patients) for atrial fibrillation in addition to guidelines-based therapy for heart failure. All the patients had New York Heart Association class II, III, or IV heart failure, a left ventricular ejection fraction of 35% or less, and an implanted defibrillator. The primary end point was a composite of death from any cause or hospitalization for worsening heart failure.

RESULTS

After a median follow-up of 37.8 months, the primary composite end point occurred in significantly fewer patients in the ablation group than in the medical-therapy group (51 patients [28.5%] vs. 82 patients [44.6%]; hazard ratio, 0.62; 95% confidence interval [CI], 0.43 to 0.87; P=0.007). Significantly fewer patients in the ablation group died from any cause (24 [13.4%] vs. 46 [25.0%]; hazard ratio, 0.53; 95% CI, 0.32 to 0.86; P=0.01), were hospitalized for worsening heart failure (37 [20.7%] vs. 66 [35.9%]; hazard ratio, 0.56; 95% CI, 0.37 to 0.83; P=0.004), or died from cardiovascular causes (20 [11.2%] vs. 41 [22.3%]; hazard ratio, 0.49; 95% CI, 0.29 to 0.84; P=0.009).

CONCLUSIONS

Catheter ablation for atrial fibrillation in patients with heart failure was associated with a significantly lower rate of a composite end point of death from any cause or hospitalization for worsening heart failure than was medical therapy. (Funded by Biotronik; CASTLE-AF ClinicalTrials.gov number, NCT00643188.)

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This article was last updated on February 5, 2018, at NEJM.org.

N Engl J Med 2018;378:417-27.
DOI: 10.1056/NEJMoa1707855

Atrial fibrillation and heart failure are common coexisting conditions,[1,2] with atrial fibrillation increasing the risk of stroke, hospitalization for heart failure, and death.[3-6] Although the treatment of atrial fibrillation can substantially alter long-term outcomes in patients with heart failure, the subject of what is the most effective management strategy is debated.

Rhythm control with antiarrhythmic drugs is not superior to rate control in patients with coexisting heart failure and atrial fibrillation.[7] Catheter ablation is a well-established option for symptomatic atrial fibrillation that is resistant to drug therapy in patients with otherwise normal cardiac function,[8-12] and various studies have shown that ablation is associated with positive outcomes in patients with heart failure.[13-17] Nevertheless, the effectiveness of catheter ablation in improving rates of hard primary end points such as death or the progression of heart failure has not been tested in large, randomized, controlled trials, and guidelines provide no clear consensus regarding the best management approach.[6,11,18,19] We initiated the Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF) trial to address this issue.[20]

Methods

Study Design and Oversight

CASTLE-AF is a multicenter, open-label, randomized, controlled trial that was conducted to assess whether catheter ablation lowers morbidity and mortality as compared with medical therapy (rate or rhythm control) in patients with coexisting atrial fibrillation and medically managed heart failure. The trial rationale, design, and protocol have been described previously.[20] The protocol is available with the full text of this article at NEJM.org.

The executive committee and the steering committee designed the trial. (For details, see the Supplementary Appendix, available at NEJM.org.) The trial was approved by the ethics committee at each participating center. Data management and evaluation were provided by the Center for Clinical Research, and the statistical analysis was performed by the Institute of Medical Statistics and Computational Biology (both in Cologne, Germany). The trial was sponsored by Biotronik, which assisted with data management and quality control of the statistical analysis but had no role in the design of the trial or the execution of the design. All the authors vouch for the completeness and accuracy of the data and the analyses and for the fidelity of the trial to the protocol. The first author made the decision to submit the manuscript for publication.

Patient Selection

Patients with heart failure and a history of symptomatic atrial fibrillation were screened. To be enrolled in the trial, patients had to have paroxysmal or persistent atrial fibrillation; an absence of response to, unacceptable side effects from, or unwillingness to take antiarrhythmic drugs; and New York Heart Association (NYHA) class II, III, or IV heart failure and a left ventricular ejection fraction (LVEF) of 35% or less. In addition, to facilitate detection of recurrence of atrial fibrillation, all the patients were required to have had implantation of a Biotronik-manufactured implantable cardioverter–defibrillator (ICD) device or a cardiac resynchronization therapy defibrillator (CRT-D) with automatic daily remote-monitoring capabilities. Major exclusion criteria were candidacy for heart transplantation or planned cardiovascular intervention. (A complete list of the exclusion criteria is provided in the Supplementary Appendix.) All the patients provided written informed consent.

Randomization, Run-in Phase, and Baseline Evaluation

The patients were enrolled and randomly assigned in a 1:1 ratio to receive catheter ablation or medical therapy for atrial fibrillation. A computerized central randomization design was generated and stratified according to center, type of atrial fibrillation (paroxysmal or persistent), type of implantable device (ICD or CRT-D), and ICD indication.

A run-in phase of 5 weeks was used to adjust the administration of medications for heart failure in accordance with the latest guidelines. After the run-in period, a baseline evaluation was performed, and patients were referred for either catheter ablation or medical therapy for atrial fibrillation according to the randomization design. Details regarding this phase are provided in the Supplementary Appendix.

Catheter Ablation

The aim of the ablation procedure was to achieve isolation of all pulmonary veins and to

restore sinus rhythm (see the Supplementary Appendix). Additional ablation lesions were made at the discretion of the operators. All the operators had performed at least 50 ablation procedures and were allowed to use their preferred ablation system. Left atrial thrombus was ruled out by means of transesophageal echocardiography before all procedures; if a thrombus was present, ablation was postponed until the thrombus in the left atrial appendage had dissolved, as documented on repeat transesophageal echocardiography. After ablation, all the patients received warfarin for at least 6 months; treatment thereafter was extended at the discretion of the treating physician.[20]

MEDICAL TREATMENT OF ATRIAL FIBRILLATION

The medical therapy for atrial fibrillation was administered in accordance with the guidelines that were available at the time of the trial.[12,21] Efforts to maintain sinus rhythm were recommended. Among patients who were treated for rate control, the recommended criteria varied according to the age of the patient. The aim of the treatment was a ventricular rate of 60 to 80 beats per minute at rest and 90 to 115 beats per minute during moderate exercise.

FOLLOW-UP

For all patients, the Biotronik Home Monitoring option was activated to monitor the recurrence of atrial fibrillation (see the text and Fig. S1 in the Supplementary Appendix). Recurrence was defined as any episode of atrial arrhythmia that lasted longer than 30 seconds, in accordance with the 2012 consensus statement from the Heart Rhythm Society and others.[22] If atrial fibrillation recurred, a repeat ablation was recommended unless contraindicated clinically.

During regular follow-up visits at 3, 6, 12, 24, 36, 48, and 60 months after baseline, patients' ICDs or CRT-Ds were checked, adverse events were documented, echocardiographic measurements were obtained, and a 6-minute walking test was conducted, in addition to other procedures, which are listed in the Supplementary Appendix.

STUDY OUTCOMES

The primary end point was a composite of death from any cause or worsening of heart failure that led to an unplanned overnight hospitalization. Major secondary end points were death from any cause, unplanned hospitalization related to heart failure, death from cardiovascular disease, cerebrovascular accident, unplanned hospitalization for cardiovascular disease, and any hospitalization. In the ablation group, procedure-related adverse events and atrial fibrillation-free intervals were also assessed. Definitions of clinical end points are provided in the Supplementary Appendix. All end-point events were adjudicated by an independent committee whose members were unaware of treatment assignments.

STATISTICAL ANALYSIS

A three-stage adaptive group sequential design was used. A total of 65, 130, and 195 primary end-point events were required at the time of the first two interim analyses and the final analysis, respectively, to provide a total power of 80% to detect a hazard ratio of 0.67 for the primary end point in the ablation group versus the medical group, with an overall two-sided alpha level of 0.05.[20] The trial was continued as planned after the first interim analysis. However, both the rate of trial enrollment and the rate of primary end-point events were lower than anticipated, and as the trial proceeded it became evident that the final target of 195 primary end-point events was unlikely to be reached within a reasonable time frame. Thus, the second interim analysis was not conducted as planned, and the trial was stopped in December 2016 after 133 primary end-point events had occurred. (For details, see the Supplementary Appendix.) The overall two-sided alpha level of 0.05 was maintained with the use of the conditional rejection probability approach proposed by Müller and Schäfer.[23]

The treatment groups were compared on a modified intention-to-treat basis. This analysis excluded patients who had died or were withdrawn from the trial during the run-in period. It also excluded end-point events occurring during the run-in period and included only deaths and not other events during the first 12 weeks after the baseline visit (the "blanking period" after ablation, with an identical period of event exclusion after baseline in the medical-therapy group). Several sensitivity analyses were also performed.

Distributions of quantitative variables are described as means (±SD) or by median and interquartile range and compared with the use of the Mann–Whitney U test. Qualitative variables

are summarized by count and percentage and compared with the use of the chi-square test. To calculate the change from baseline over time, missing values for continuous outcomes were imputed with the use of the last observation carried forward, with post hoc confirmation achieved by means of multiple imputation. Clinical outcomes were examined with the use of time-to-first-event analysis. Differences in time-to-event distributions were evaluated by means of the log-rank test. In addition, hazard ratios with 95% confidence intervals and P values from Cox regression analyses and from corresponding Wald statistics have been provided.

Data were managed with the SPSS statistical package, version 23 (IBM). A two-sided P value of less than 0.05 was considered to indicate statistical significance. No adjustment for multiple testing was performed. All the analyses except those related to the primary end point were considered to be exploratory.

Figure 1 (facing page). Trial Flow Chart.

A total of 3013 patients were assessed for eligibility; 2615 patients were excluded because they did not meet the criteria for inclusion or did meet the criteria for exclusion (for details, see the Supplementary Appendix. Patients underwent randomization at the time of enrollment. However, allocation to treatment groups on the basis of randomization was performed at the baseline visit after the run-in period and after reevaluation to determine whether the patient had an acute coronary syndrome, had undergone cardiac surgery, angioplasty, or stroke since enrollment, had been listed for heart transplantation, or had a new requirement for dialysis owing to terminal renal failure, since all such patients are designated as having been withdrawn in accordance with the protocol. After the baseline visit, 363 patients remained in the trial and were included in the primary analysis. In the medical-therapy group, 18 patients did not receive the allocated intervention and underwent catheter ablation during the trial. In the ablation group, 28 patients did not receive the allocated intervention for the indicated reasons. Medical reasons for exclusion included extensive left atrial scarring, the need for mitral-valve replacement before ablation (absence of the capacity to comply within the window of time allotted for ablation), diagnosis of cancer, or the absence of a suitable vein for puncture. Patients who were lost to follow-up were those who did not attend the most recently scheduled follow-up visit (with or without attendance at previous follow-up visits). LAA denotes left atrial appendage.

RESULTS

ASSESSMENT AND EVALUATION

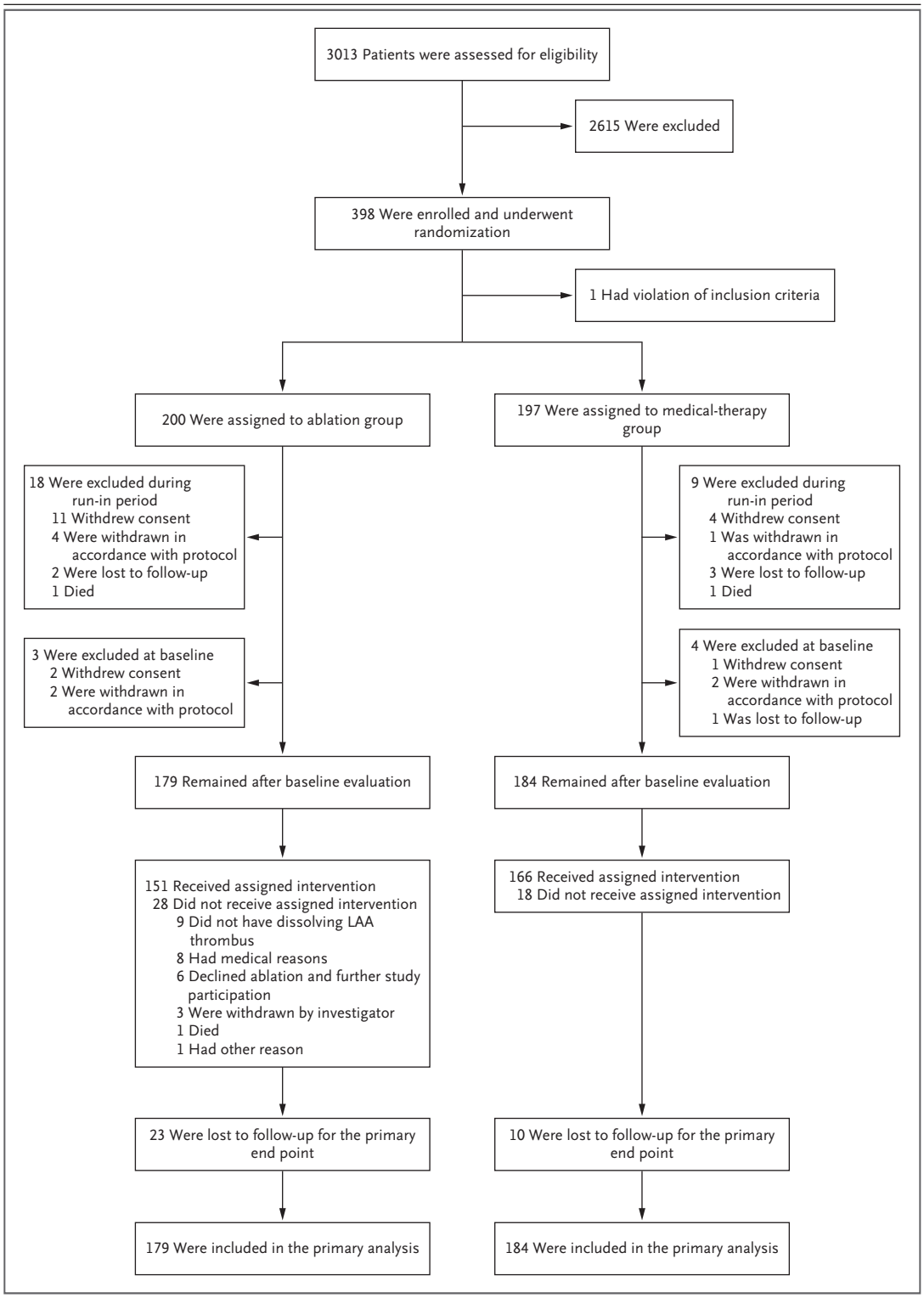
From January 2008 through January 2016, a total of 3013 patients were assessed for eligibility and 398 were enrolled at 33 sites in Europe, Australia, and the United States (Fig. 1, and Fig. S2 in the Supplementary Appendix). At the baseline evaluation 5 weeks after enrollment, 363 patients remained in the trial, including 179 patients who were randomly assigned to undergo ablation and 184 patients who were randomly assigned to receive medical therapy for atrial fibrillation. A total of 34 patients were excluded for the reasons listed in Figure 1. Baseline characteristics are shown in Table 1 and in Tables S1 through S4 in the Supplementary Appendix.

FOLLOW-UP PERIOD AND CROSSOVER

The mean duration of the follow-up period was 37.6±20.4 months (median, 38.7 months; interquartile range, 22.3 to 60.0) in the ablation group and 37.4±17.7 months (median, 37.0 months; interquartile range, 24.4 to 55.9) in the medical-therapy group. Of the 179 patients who were assigned to the ablation group, 151 (84.4%) received the assigned treatment (average number of ablation procedures per patient, 1.3±0.5) and 28 (15.6%) crossed over to medical therapy for the reasons listed in Figure 1. Of the 151 patients who underwent ablation, all pulmonary veins were successfully isolated in 149 patients (98.7%); additional lesions were created in 77 of these patients (51.7%). Repeat ablations were performed 427±354 days after the initial ablation in 37 patients (24.5%) (Table S5 in the Supplementary Appendix). Of the 184 patients in the medical-therapy group, 18 patients (9.8%) crossed over to catheter ablation 268±270 days after baseline. A rhythm-control strategy was used in approximately 30% of the patients in the medical-therapy group (Fig. S3 in the Supplementary Appendix).

PRIMARY END POINT

The composite primary end point — death or hospitalization for worsening heart failure — occurred in significantly fewer patients in the ablation group than in the medical-therapy group (51 patients [28.5%] vs. 82 patients [44.6%]; P=0.006 by the log-rank test) (Table 2). In addition, without consideration of the group sequential design, the analysis showed that the rate of the primary end point was significantly lower in the ablation group than in the medical-therapy group (hazard ratio, 0.62; 95% confidence interval [CI], 0.43 to 0.87; P=0.007 by Cox regression).



The number of patients who would need to be treated to prevent the primary end point at 36 months was 8.3. Kaplan–Meier curves showing a comparison of the primary end points in the two trial groups are provided in Figure 2A. The Kaplan–Meier event-rate estimates at 60 months were 38.0% in the ablation group and 54.8% in the medical-therapy group (Table S6 in the

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Treatment Type	
	Ablation (N=179)	Medical Therapy (N=184)
Age — yr		
Median	64	64
Range	56–71	56–73.5
Male sex — no. (%)	156 (87)	155 (84)
Body-mass index†		
Median	29.0	29.1
Range	25.9–32.2	25.9–32.3
New York Heart Association class — no./total no. (%)		
I	20/174 (11)	19/179 (11)
II	101/174 (58)	109/179 (61)
III	50/174 (29)	49/179 (27)
IV	3/174 (2)	2/179 (1)
Cause of heart failure — no. (%)‡		
Ischemic	72 (40)	96 (52)
Nonischemic	107 (60)	88 (48)
Type of atrial fibrillation — no. (%)		
Paroxysmal	54 (30)	64 (35)
Persistent	125 (70)	120 (65)
Long-standing persistent (duration >1 year)	51 (28)	55 (30)
Left atrial diameter		
Total no. of patients evaluated	162	172
Median — mm	48.0	49.5
Interquartile range — mm	45.0–54.0	5.0–55.0
Left ventricular ejection fraction		
Total no. of patients evaluated	164	172
Median — %	32.5	31.5
Interquartile range — %	25.0–38.0	27.0–37.0
CRT-D implanted — no. (%)§	48 (27)	52 (28)
ICD implanted — no. (%)§	131 (73)	132 (72)
Dual-chamber	128 (72)	123 (67)
Single-lead device with "floating" atrial sensing dipole	3 (2)	9 (5)
Indication for ICD implantation — no. (%)		
Primary prevention	160 (89)	163 (89)
Secondary prevention	19 (11)	21 (11)
History of amiodarone use — no./total no. (%)¶		
Failure	78/175 (45)	82/176 (47)
Unacceptable side effects	21/175 (12)	24/176 (14)
Nonuse	76/175 (43)	70/176 (40)

* Baseline evaluation was performed after the run-in period, which continued for 5 weeks after enrollment. Characteristics at the time of enrollment are shown in Table S1 (for patients who reached the baseline evaluation and were included in the primary analysis) and Table S2 (for patients who underwent randomization), medications at baseline and last follow-up in Table S3, and additional baseline characteristics in Table S4, all in the Supplementary Appendix. CRT-D denotes cardiac resynchronization therapy defibrillator and ICD implantable cardioverter–defibrillator.

† Body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ There was a significant difference between the two groups regarding the cause of heart failure (P=0.022).

§ In all the patients, devices were implanted before enrollment.

¶ Data on the history of use of more than one antiarrhythmic agent were not collected. Failure indicates recurrence of atrial fibrillation despite receipt of a therapeutic dose, and nonuse indicates patient unwillingness to take the drug owing to concern about possible side effects or contraindications as explained by the physician.

Table 2. Primary and Secondary Clinical End Points.*

End Point	Ablation (N=179)	Medical Therapy (N=184)	Hazard Ratio (95% CI)	P Value	
				Cox Regression	Log-Rank Test
	number (percent)				
Primary†	51 (28.5)	82 (44.6)	0.62 (0.43–0.87)	0.007	0.006
Secondary					
Death from any cause	24 (13.4)	46 (25.0)	0.53 (0.32–0.86)	0.01	0.009
Heart-failure hospitalization	37 (20.7)	66 (35.9)	0.56 (0.37–0.83)	0.004	0.004
Cardiovascular death	20 (11.2)	41 (22.3)	0.49 (0.29–0.84)	0.009	0.008
Cardiovascular hospitalization	64 (35.8)	89 (48.4)	0.72 (0.52–0.99)	0.04	0.04
Hospitalization for any cause	114 (63.7)	122 (66.3)	0.99 (0.77–1.28)	0.96	0.96
Cerebrovascular accident	5 (2.8)	11 (6.0)	0.46 (0.16–1.33)	0.15	0.14

* All numbers and percentages represent the total numbers of events and raw event rates after a median follow-up of 37.8 months. Deaths and cerebrovascular accidents were evaluated at baseline and 12 weeks after baseline for hospitalizations in the two groups (the "blanking period"). For Kaplan–Meier estimates at 12, 36, and 60 months, see Table S6 in the Supplementary Appendix.
† The primary end point is a composite of death from any cause or hospitalization for worsening heart failure.

Supplementary Appendix). The primary outcome in subgroups of interest is shown in Figure 3. The results of various sensitivity analyses of the primary end point were all consistent with the results of the primary analysis (Table S7 in the Supplementary Appendix).

SECONDARY END POINTS

All secondary analyses were considered to be exploratory and were not adjusted for multiple testing. There were 24 deaths in the ablation group and 46 deaths in the medical-therapy group, with rates of 13.4% and 25.0%, respectively (hazard ratio by Cox regression, 0.53; 95% CI, 0.32 to 0.86; P=0.01). There were 37 patients with heart failure–related admissions in the ablation group and 66 patients in the medical-therapy group, with rates of 20.7% and 35.9%, respectively (hazard ratio for event in the Cox regression model, 0.56; 95% CI, 0.37 to 0.83; P=0.004). The Kaplan–Meier curves for these end points are presented in Figure 2B and 2C.

There were 20 cardiovascular deaths (11.2%) in the ablation group and 41 (22.3%) in the medical-therapy group (hazard ratio, 0.49; 95% CI, 0.29 to 0.84; P=0.009). Data for additional secondary clinical end points are presented in Table 2, and in Figures S4 and S5 in the Supplementary Appendix. Kaplan–Meier event-rate estimates at 12, 36, and 60 months are shown in Table S6 in the Supplementary Appendix.

OTHER OUTCOMES

The median absolute increase in LVEF from baseline to the 60-month follow-up visit was 8.0% (interquartile range, 2.2 to 19.1) in the ablation group and was 0.2% (–3.0 to 16.1) in the medical-therapy group (P=0.005). A post-ablation LVEF of 35% or higher was measured in 104 patients in the ablation group (68.0%) and in 50.0% of the 18 patients in the medical-therapy group who crossed over to the ablation group (median LVEF, 43.3% and 37.1%, respectively). The median improvement in LVEF in the ablation group was 7.3 percentage points at 60 months for patients with paroxysmal atrial fibrillation and 10.1 percentage points for patients with persistent atrial fibrillation. Trends in LVEF, 6-minute walk distance, and left atrial diameter during follow-up, which were calculated by means of the last-observation-carried-forward method and with multiple imputation, are shown in Tables S8A and S8B, respectively, in the Supplementary Appendix.

On the basis of the data extracted from the memory of the implanted devices, 63.1% of the patients in the ablation group and 21.7% in the medical-therapy group (P<0.001) were in sinus rhythm at the 60-month follow-up visit and had not had recurrence of atrial fibrillation since the previous follow-up visit (typically at 48 months). The adjudicated rate of recurrence of atrial fibrillation in the ablation group among those who

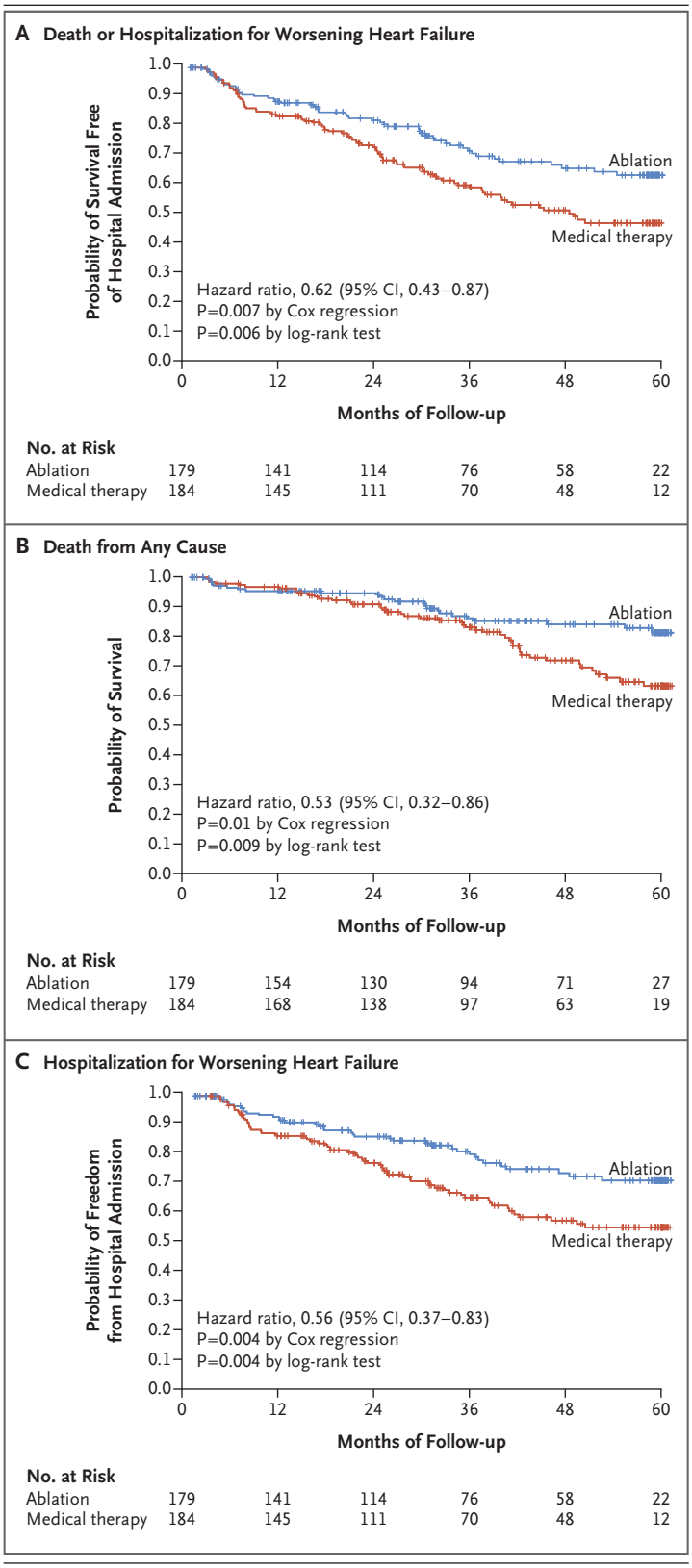


Figure 2. Kaplan–Meier Curves Comparing Survival Free of the Primary End Point (Death from Any Cause or Admission for Worsening Heart Failure) and Its Two Components in the Two Trial Groups.

Day 0 is the time of the baseline visit. Panel A shows the probability of freedom from death from any cause or admission for worsening heart failure, Panel B the probability of freedom from death from any cause, and Panel C the probability of freedom from admission for worsening heart failure.

had actually undergone ablation and who were followed for up to 60 months was 50.0% (75 of 151 patients), with an average of 1.3±0.5 ablation procedures per treated patient. The atrial fibrillation burden is described in Tables S9 and S10 and Figures S6 and S7 in the Supplementary Appendix.

PROCEDURAL COMPLICATIONS AND SERIOUS ADVERSE EVENTS

Three patients in the ablation group had pericardial effusion, and one of these patients required pericardiocentesis. Three patients had severe bleeding that required blood transfusion (with two bleeding episodes from femoral puncture sites and one pseudoaneurysm, which was corrected surgically). Asymptomatic pulmonary-vein stenosis was diagnosed in one patient at follow-up. Other complications and serious adverse events in the two trial groups are listed in Table S11 in the Supplementary Appendix.

DISCUSSION

In the CASTLE-AF trial, we found that the use of ablation for atrial fibrillation in patients with heart failure was associated with a significantly lower rate of a composite of death and hospitalization for heart failure than medical therapy. We also found that there was a benefit in all-cause mortality alone, which was driven by a significantly lower rate of cardiovascular death in the ablation group. Furthermore, catheter ablation reduced the burden of atrial fibrillation, increased the distance walked in 6 minutes, and improved the LVEF.

Several trials have reported improvements in soft end points with catheter ablation. In the PABA-CHF (Pulmonary Vein Antrum Isolation

Subgroup	Ablation	Medical Therapy	Hazard Ratio (95% CI)	P Value for Interaction
	no. of events/no. of patients			
Type of atrial fibrillation				0.90
Paroxysmal	17/54	34/64	0.60 (0.34–1.08)	
Persistent	34/125	48/120	0.64 (0.41–0.99)	
CRT–D implanted				0.60
No	37/131	57/132	0.65 (0.43–0.98)	
Yes	14/48	25/52	0.54 (0.28–1.04)	
ICD indication				0.20
Primary	43/160	72/163	0.57 (0.39–0.83)	
Secondary	8/19	10/21	1.03 (0.41–2.62)	
Sex				0.36
Female	9/23	12/29	0.93 (0.39–2.21)	
Male	42/156	70/155	0.58 (0.39–0.84)	
Age				0.17
<65 yr	18/96	34/99	0.48 (0.27–0.85)	
≥65 yr	33/83	48/85	0.79 (0.50–1.23)	
NYHA functional class				0.06
II	20/101	46/109	0.42 (0.25–0.72)	
III	22/50	26/49	0.89 (0.51–1.58)	
LVEF				0.01
<25%	20/34	15/27	1.36 (0.69–2.65)	
≥25%	29/130	61/145	0.48 (0.31–0.74)	
Cause of heart failure				0.56
Nonischemic	26/107	29/88	0.74 (0.43–1.25)	
Ischemic	25/72	53/96	0.60 (0.37–0.97)	
Diabetes				0.06
No	32/136	48/117	0.52 (0.33–0.81)	
Yes	19/43	34/67	1.01 (0.58–1.78)	
Hypertension				0.88
No	12/50	19/48	0.59 (0.28–1.21)	
Yes	39/129	63/136	0.63 (0.42–0.93)	
Amiodarone use				0.66
No	37/122	61/133	0.65 (0.43–0.97)	
Yes	13/55	18/46	0.55 (0.27–1.13)	
Digitalis use				0.68
No	41/146	52/124	0.65 (0.43–0.98)	
Yes	9/31	27/56	0.56 (0.26–1.19)	
Beta-blocker use				0.47
No	4/12	4/9	1.01 (0.25–4.05)	
Yes	46/165	75/171	0.60 (0.42–0.87)	

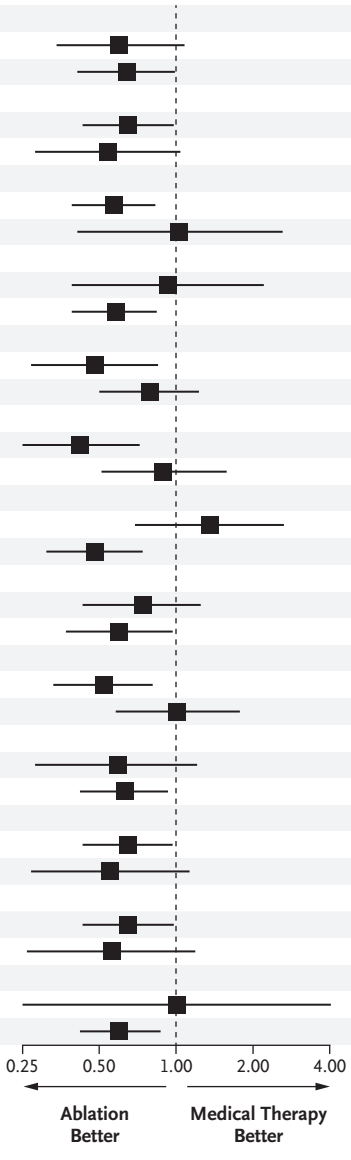


Figure 3. Subgroup Analyses of the Primary End Point.

Hazard ratios and P values for interaction are based on Cox logistic-regression analyses. There was a significant interaction between left ventricular ejection fraction (LVEF) and the primary end point (death from any cause or admission for worsening heart failure), which implies that patients with an LVEF of 25% or more were more likely to have a benefit from ablation for atrial fibrillation than those with an LVEF of less than 25%. CRT-D denotes cardiac resynchronization therapy defibrillator, ICD implantable cardioverter–defibrillator, and NYHA New York Heart Association.

versus AV Node Ablation with Bi-Ventricular Pacing for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure) trial, investigators reported the superiority of ablation in the composite end point of LVEF, 6-minute walk distance, and quality of life as compared with

atrioventricular-junction ablation combined with cardiac resynchronization therapy.[13] The CAMTAF (Catheter Ablation versus Medical Treatment of AF in Heart Failure) trial showed an improvement in LVEF with ablation in patients with persistent atrial fibrillation.[24] More recently, the AATAC (Ablation versus Amiodarone for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted ICD) trial showed that ablation was superior to amiodarone in maintaining sinus rhythm and improving LVEF in patients with persistent atrial fibrillation. The trial also showed a favorable effect on rates of death and hospitalization for heart failure.[17]

In the CASTLE-AF trial, in contrast to previous trials, we evaluated the hard primary end point of death or hospitalization for heart failure. Moreover, patients were followed for a period to assess long-term outcomes. The mortality benefit of ablation in our trial did not emerge until after 3 years (Fig. 2B). We also included patients with both paroxysmal and persistent atrial fibrillation and found that both groups benefited from catheter ablation (Fig. 3). We avoided mandating a specific strategy (rate control vs. rhythm control) or choice of antiarrhythmic drugs in the medical-therapy group, since previous studies had not shown one strategy or drug to be superior to another.[7,25,26]

Previous trials cast skepticism over the mortality benefit of sinus-rhythm maintenance in patients with and without heart failure.[7,25,26] The AF-CHF (Atrial Fibrillation and Congestive Heart Failure) trial and the DIAMOND-CHF (Danish Investigators of Arrhythmia and Mortality on Dofetilide in Congestive Heart Failure) trial compared the strategies of rate control with rhythm control to treat atrial fibrillation in patients with heart failure with antiarrhythmic drugs.[7,26] The antiarrhythmic drug of choice was predominantly amiodarone in the AF-CHF trial and exclusively dofetilide in the DIAMOND-CHF trial. These trials concluded that neither drug was associated with lower mortality in patients with coexisting atrial fibrillation and heart failure despite a lowering of the atrial fibrillation burden.[27-31] In contrast, pursuing rhythm control with catheter ablation proved to be of significant benefit with regard to outcomes in the CASTLE-AF trial. In the ablation group, 63% of patients were in sinus rhythm at 60 months versus 22% in the medical-therapy group, which suggests that maintenance of sinus rhythm is beneficial when achieved without the use of antiarrhythmic drugs.

One of the limitations of our trial is the lack of blinding with regard to randomization and treatment. It would have been quite difficult to perform a truly blinded trial with a sham ablation procedure, but the lack of blinding could have led to bias in such decisions as whether to admit a patient for worsening heart failure. All the patients had an ICD or CRT-D, which may have affected overall mortality in the two groups. A greater number of patients in the ablation group than in the medical-therapy group crossed over to the other treatment group, but the results of per-protocol and as-treated analyses were similar to those of the primary analysis. Finally, although medical therapy (for both atrial fibrillation and heart failure) was managed systematically, we cannot exclude the possibility that a different or more aggressive approach to medical management might have influenced the trial results.

In conclusion, in a comparison of catheter ablation with medical therapy in patients with heart failure and atrial fibrillation, we found that catheter ablation was associated with lower rates of death from any cause and lower rates of hospital admission for heart failure along with reducing the burden of atrial fibrillation and improving the LVEF.

Supported by Biotronik.

Dr. Marrouche reports receiving grant support and consulting fees from Abbott, Wavelet Health, Medtronic, Vytronus, Biosense Webster, Boston Scientific, GE Health Care, and Siemens, receiving consulting fees from Preventice, and holding equity in Marrek and Cardiac Design; Dr. Brachmann, receiving consulting fees from Abbott, St. Jude Medical, Medtronic, Bayer, Livanova, Pfizer, Boston Scientific, Boehringer Ingelheim, and Biotronik; Dr. Boersma, receiving consulting fees, paid to his institution, from Medtronic and Boston Scientific; Dr. Jordaens, receiving consulting fees from Biotronik Belgium, fees for serving on a steering board from Biotronik Germany, and lecture fees and travel support from Boston Scientific Belgium; Dr. Merkely, receiving grant support from Boston Scientific and lecture fees from Medtronic, Biotronik, St. Jude Medical, and Terumo; Dr. Sanders, receiving grant support from, serving on an advisory board for, and receiving consulting fees from St. Jude Medical, Boston Scientific, and Medtronic, receiving grant support from and serving on an advisory board for Biosense-Webster, serving on an advisory board for CathRx, and receiving grant support from Biotronik and Liva Nova; Dr. Proff, being employed by Biotronik; and Dr. Bänsch, receiving consulting fees from Biotronik. No other potential conflict of interest relevant to this article was reported.

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

We thank Mobin Kheirkhahan, Simone Frömer, Beate Wenzel, Hartmut Stützer, Bernd Brüsehaber, Sandra Willms, Christian Mahnkopf, Dejan Danilovic, Nazem Akoum, Alex Baher, and Christopher McGann.

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