ORIGINAL ARTICLE

# Catheter Ablation in End-Stage Heart Failure with Atrial Fibrillation

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## ABSTRACT

### BACKGROUND

The role of catheter ablation in patients with symptomatic atrial fibrillation and end-stage heart failure is unknown.

### METHODS

We conducted a single-center, open-label trial in Germany that involved patients with symptomatic atrial fibrillation and end-stage heart failure who were referred for heart transplantation evaluation. Patients were assigned to receive catheter ablation and guideline-directed medical therapy or medical therapy alone. The primary end point was a composite of death from any cause, implantation of a left ventricular assist device, or urgent heart transplantation.

### RESULTS

A total of 97 patients were assigned to the ablation group and 97 to the medical-therapy group. The trial was stopped for efficacy by the data and safety monitoring board 1 year after randomization was completed. Catheter ablation was performed in 81 of 97 patients (84%) in the ablation group and in 16 of 97 patients (16%) in the medical-therapy group. After a median follow-up of 18.0 months (interquartile range, 14.6 to 22.6), a primary end-point event had occurred in 8 patients (8%) in the ablation group and in 29 patients (30%) in the medical-therapy group (hazard ratio, 0.24; 95% confidence interval [CI], 0.11 to 0.52; P<0.001). Death from any cause occurred in 6 patients (6%) in the ablation group and in 19 patients (20%) in the medical-therapy group (hazard ratio, 0.29; 95% CI, 0.12 to 0.72). Procedure-related complications occurred in 3 patients in the ablation group and in 1 patient in the medical-therapy group.

### CONCLUSIONS

Among patients with atrial fibrillation and end-stage heart failure, the combination of catheter ablation and guideline-directed medical therapy was associated with a lower likelihood of a composite of death from any cause, implantation of a left ventricular assist device, or urgent heart transplantation than medical therapy alone. (Funded by Else Kröner-Fresenius-Stiftung; CASTLE-HTx ClinicalTrials.gov number, NCT04649801.)

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In patients with advanced end-stage heart failure, timely referrals for heart transplantation and implantation of a left ventricular assist device are essential to achieve favorable outcomes. Patients with heart failure and symptomatic atrial fibrillation who undergo catheter ablation have a lower likelihood of death or worsening heart failure than those who do not.[1-4] Data from prospective randomized trials on the effectiveness of catheter ablation in improving these outcomes in patients with end-stage heart failure are lacking, and professional society guidelines do not provide recommendations regarding the appropriate strategy to manage atrial fibrillation in these patients. We conducted the randomized CASTLE-HTx (Catheter Ablation for Atrial Fibrillation in Patients with End-Stage Heart Failure and Eligibility for Heart Transplantation) trial to assess the safety and efficacy of catheter ablation in patients with end-stage heart failure and symptomatic atrial fibrillation who were referred to our center for evaluation for heart transplantation or implantation of a left ventricular assist device.

## Methods

### Trial Design and Oversight

CASTLE-HTx was a single-center, open-label, investigator-initiated, superiority, randomized clinical trial. The rationale for and design of the trial have been published previously.[5] This trial was conducted at Herz- und Diabeteszentrum Nordrhein-Westfalen (Bad Oeynhausen, Germany), a referral center for heart transplantation with an annual volume of approximately 80 transplantations and a total volume of approximately 3000 since 1989.[6] The trial was supported by an unrestricted educational grant from Else Kröner-Fresenius-Stiftung, a foundation that had no role in the design or execution of the trial or in the preparation of the manuscript. The German health insurance system covered all costs related to catheter ablation, including materials.

Investigators who were affiliated with Herz- und Diabeteszentrum Nordrhein-Westfalen, Ruhr-Universität Bochum, designed the trial, collected and managed the data, and performed the statistical analyses (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial was approved by the institutional review board at Ruhr-Universität Bochum, and all the patients provided written informed consent. An independent data and safety monitoring board oversaw the trial and reviewed accumulated trial outcomes to safeguard the well-being of the patients. The authors had unrestricted access to the data and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, which is available at NEJM.org. The first author made the decision to submit the manuscript for publication.

### Patients

Patients with end-stage heart failure and symptomatic atrial fibrillation who were referred for assessment of eligibility for heart transplantation or implantation of a left ventricular assist device with the use of the International Society for Heart and Lung Transplantation listing criteria and the position statement of the Heart Failure Association of the European Society of Cardiology were screened for inclusion in the trial.[7,8] To be eligible for enrollment, patients had to have symptomatic atrial fibrillation, New York Heart Association class II or higher heart failure, a left ventricular ejection fraction of 35% or less, and impaired functional capacity, as assessed with the use of the 6-minute walk test. At the time of randomization, all the patients had to be in a clinically stable condition. In addition, all the patients had an implantable cardiac device with activated arrhythmia detection allowing for continuous rhythm monitoring to ensure prompt management of rhythm or rate in the event of arrhythmia recurrence. Details on the representativeness of trial patients are provided in Table S1, and a complete list of enrollment inclusion and exclusion criteria is provided in Table S2.

### Randomization

The investigational site scheduled the date for enrollment and baseline testing after verifying the inclusion and exclusion criteria and documenting demographic data and medical history. Patients were randomly assigned in a 1:1 ratio to receive either catheter ablation and guideline-directed medical therapy or medical therapy alone. Randomization was performed by means of computed block randomization.

### Interventions

Patients who presented with symptomatic atrial fibrillation who were assigned to the ablation group underwent direct current cardioversion af-

ter the transseptal puncture. If this was not successful, the catheter-ablation procedure was started with the patient in atrial fibrillation, and direct-current cardioversion was attempted after ablation around the pulmonary veins. The aim was to achieve electrical isolation of all pulmonary veins and to restore sinus rhythm. Ablation beyond the pulmonary veins was performed at the discretion of the operators. If atrial fibrillation recurred in patients assigned to the ablation group, additional ablation procedures were recommended on the basis of clinical judgment. All catheter-ablation procedures were performed by two operators who had performed at least 400 such procedures. Antiarrhythmic medication for atrial fibrillation was discontinued after ablation and could be reinitiated in case of an arrhythmia recurrence at the discretion of the treating physician.

Patients who were assigned to receive medical therapy only for atrial fibrillation were treated in accordance with the guidelines of American Heart Association–American College of Cardiology–Heart Rhythm Society and the European Society of Cardiology, available at the time of initiation of the trial.[9,10] The recommendation was to maintain the patient in sinus rhythm and to maintain heart-rate control.[1]

#### FOLLOW-UP

Clinical follow-up visits were scheduled for patients every 3 months for the first year and then annually thereafter. At the follow-up visits, patients underwent echocardiography, implanted devices were interrogated, patients were interviewed by their physician on heart-failure status and arrhythmia symptoms, and adverse events were documented. Data that were available by May 16, 2023, were assessed in all the patients.

#### TRIAL END POINTS

The primary end point was a composite of death from any cause, implantation of a left ventricular assist device, or urgent heart transplantation. The secondary end points included the components of the primary end point, death from cardiovascular causes, the left ventricular ejection fraction, and the atrial fibrillation burden at 6 and 12 months (Table S4).

The cumulative duration of all atrial arrhythmia episodes, expressed as a percentage of total time in the 3 months preceding the visit, was used to calculate the atrial fibrillation burden. At 12 months, patients were classified as having persistent atrial fibrillation if they had any episodes of uninterrupted atrial fibrillation for at least 7 days during the previous 3 months or had undergone electrical cardioversion during that period. Patients were classified as being in sinus rhythm if they were without any episodes of atrial fibrillation lasting 30 seconds or more during the previous 3 months. All other patients were classified as having paroxysmal atrial fibrillation.

#### STATISTICAL ANALYSIS

Under the assumption of an annualized event rate of 20% in the medical-therapy group and a hazard ratio for a primary end-point event in the ablation group of 0.50, we calculated that a sample of 194 patients would provide the trial with 80% power at a two-sided alpha level of 0.05. The trial was designed to test whether immediate catheter ablation and medical therapy would be superior to medical therapy alone with respect to the cumulative incidence of primary end-point events at 3 years. The original plan for analysis of the primary end point was to analyze the 3-year incidence data for the primary end point with the use of the log-rank test. On May 3, 2023, approximately 1 year after enrollment was completed, the data and safety monitoring board reviewed the outcomes and recommended immediate cessation of the protocol-mandated medical-therapy group, having observed an unexpectedly large difference in the primary end-point results favoring ablation, with a (post hoc) P value of less than 0.001, which complied with the Haybittle–Peto rule. The trial leadership accepted this recommendation, which was implemented on May 16, 2023. Through an amendment to the protocol, the decision regarding whether to recommend catheter ablation was at the discretion of the cardiologist caring for the patient. Clinical follow-up of all the patients was mandated for at least 3 years after the last patient had undergone randomization. The protocol amendment also stipulated that the primary end point be analyzed with follow-up censoring by the end of the day on May 15, 2023.

The analysis of the primary and secondary end points was conducted according to the intention-to-treat principle. Cox proportional-hazards modeling was used to generate hazard ratios and

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

| Characteristic | Ablation Group (N=97) | Medical-Therapy Group (N=97) |
|---|---|---|
| Age — yr | 62±12 | 65±10 |
| Male sex — no. (%) | 85 (88) | 72 (74) |
| Body-mass index† | 28±4 | 28±5 |
| NYHA functional class — no. (%)‡ | | |
| II | 33 (34) | 28 (29) |
| III | 52 (54) | 54 (56) |
| IV | 12 (12) | 15 (15) |
| Left ventricular ejection fraction — % | 29±6 | 25±6 |
| Type of atrial fibrillation — no. (%) | | |
| Paroxysmal | 28 (29) | 31 (32) |
| Persistent | 54 (56) | 54 (56) |
| Long-standing persistent: duration of >1 yr | 15 (15) | 12 (12) |
| Duration of atrial fibrillation — yr | 4±5 | 3±4 |
| History of cardioversion — no. (%) | 64 (66) | 62 (64) |
| Heart rate — beats/min | 80±21 | 82±20 |
| Cause of heart failure — no. (%) | | |
| Ischemic | 37 (38) | 39 (40) |
| Nonischemic | 60 (62) | 58 (60) |
| Left atrial diameter — mm | 49±6 | 48±8 |
| Diabetes mellitus — no. (%) | 25 (26) | 31 (32) |
| Implantable cardiac device — no. (%) | | |
| ICD | 57 (59) | 52 (54) |
| CRT-D | 35 (36) | 38 (39) |
| Rhythm monitor | 3 (3) | 4 (4) |
| Pacemaker | 2 (2) | 3 (3) |
| N-terminal pro-BNP level | | |
| No. of patients evaluated (%) | 46 (47) | 52 (54) |
| Value — pg/ml | 3852±3261 | 4461±5191 |
| 6-Min walk test | | |
| Test performed — no. (%) | 26 (27) | 24 (25) |
| Distance — m | 308±69 | 299±66 |
| Test not feasible — no. (%) | 71 (73) | 73 (75) |
| Medications — no. (%) | | |
| Amiodarone | 44 (45) | 46 (47) |
| Beta-blocker | 93 (96) | 91 (94) |
| Diuretic | 71 (73) | 76 (78) |
| ACE inhibitor or ARB | 31 (32) | 40 (41) |
| MRA | 45 (46) | 53 (55) |
| Sacubitril–valsartan | 66 (68) | 57 (59) |
| SGLT2 inhibitor | 23 (24) | 24 (25) |

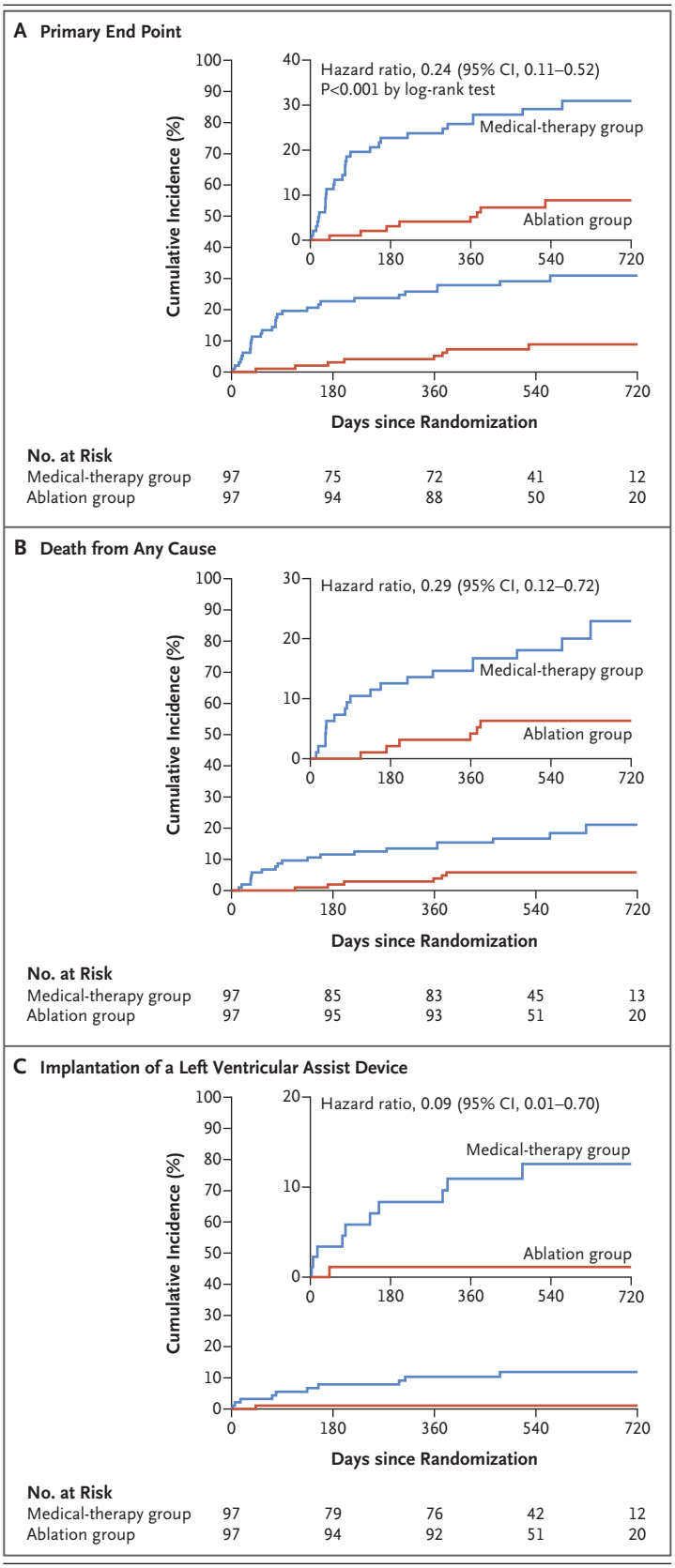
* Plus–minus values are means ±SD. Patients in the ablation group were assigned to receive catheter ablation and medical therapy, and those in the medical-therapy group were assigned to receive medical therapy alone. Baseline evaluation was performed before randomization. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, BNP B-type natriuretic peptide, CRT-D cardiac resynchronization therapy defibrillator, ICD implantable cardioverter–defibrillator, MRA mineralocorticoid-receptor antagonist, and SGLT2 sodium–glucose cotransporter 2.

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

‡ The New York Heart Association (NYHA) functional class ranges from I (no symptoms) to IV (symptoms at rest or on minimal activity).

**Figure 1. Cumulative Incidence of Trial End Points.**

Patients in the ablation group were assigned to receive catheter ablation and medical therapy, and those in the medical-therapy group were assigned to receive medical therapy alone. The primary end point was a composite of death from any cause, implantation of a left ventricular assist device, or urgent heart transplantation in the intention-to-treat population during the trial period (from the time of randomization to the end of the day on May 15, 2023). Panel A shows the results of the primary end-point analysis. The results for death from any cause are shown in Panel B, and the results for implantation of a left ventricular assist device are shown in Panel C. The insets show the same data on an enlarged y axis. Because the trial protocol did not include a provision for correction for multiplicity, statistical analyses of the secondary end points only include Kaplan–Meier curves and estimates of the (cause-specific) hazard ratios together with their 95% confidence intervals.




95% confidence intervals for the time-to-event analyses. For the end points that did not include death from any cause, the hazard ratios must be interpreted as cause-specific hazard ratios, with censoring of follow-up at the time of the competing risk event of unrelated death. The incidence of end-point events over time was analyzed with the use of Kaplan–Meier curves. The proportional-hazards assumption was not violated for the primary and secondary end-point analyses.

As of May 15, 2023, the primary end-point status of all randomly assigned patients was known, and follow-up censoring was applied. We evaluated changes at 6 and 12 months for the left ventricular ejection fraction and the atrial fibrillation burden by calculating the difference relative to baseline if both measurements were available. Using the independent t-test, we determined 95% confidence intervals for between-group differences in mean change. For the primary end point, a two-sided log-rank P value was calculated. Because the trial protocol did not include a provision for correction for multiplicity, results for secondary end points are reported as point estimates with 95% confidence intervals, without statistical testing. The widths of the confidence intervals have not been adjusted for multiplicity, so they should not be used to infer definitive treatment effects for secondary end points. Analyses were conducted with the use of SPSS Statistics software, version 29 (IBM).

**Table 2. Primary and Secondary End Points.**

| End Point | Ablation Group (N=97) | Medical-Therapy Group (N=97) | Hazard Ratio (95% CI)* | P Value† |
|---|---|---|---|---|
| | *no. (%)* | | | |
| Primary end point‡ | 8 (8) | 29 (30) | 0.24 (0.11 to 0.52) | <0.001 |
| Secondary end points | | | | |
| Death from any cause | 6 (6) | 19 (20) | 0.29 (0.12 to 0.72) | |
| Cardiovascular | 5 (5) | 18 (19) | 0.25 (0.09 to 0.68) | |
| Cerebrovascular | 0 | 1 (1) | | |
| Cancer | 1 (1) | 0 | | |
| Death after nonfatal primary end point | 0 | 5 (5) | | |
| Implantation of left ventricular assist device | 1 (1) | 10 (10) | 0.09 (0.01 to 0.70) | |
| Urgent heart transplantation | 1 (1) | 6 (6) | 0.15 (0.02 to 1.25) | |

* Because the trial protocol did not include a provision for correction for multiplicity, results for secondary end points are reported as point estimates with 95% confidence intervals, without further statistical testing. The widths of the confidence intervals have not been adjusted for multiplicity, so they should not be used to infer definitive treatment effects for secondary end points.
† The P value was calculated from a two-sided log-rank test.
‡ The primary end point is composite of death from any cause, implantation of a left ventricular assist device, or urgent heart transplantation.

## RESULTS

### PATIENTS

From November 2020 through May 2022, a total of 97 patients were randomly assigned to the ablation group and 97 to the medical-therapy group. The baseline characteristics of the two groups are shown in Table 1.

Ablation was performed in 81 of 97 patients (84%) in the ablation group and in 16 of 97 patients (16%) in the medical-therapy group (Table S3 and Fig. S1). Of the 97 patients assigned to the ablation group, 81 underwent ablation at a median of 20.0 days after randomization (interquartile range, 2.0 to 55.5). Details of when catheter ablation was performed are provided in Figure S2. In the ablation group, 51 patients underwent pulmonary-vein isolation alone and 30 patients underwent pulmonary-vein ablation as well as ablation of other areas. Nine patients (9%) underwent multiple catheter-ablation procedures. A total of 16 patients (16%) in the medical-therapy group underwent a catheter-ablation procedure. There were 4 procedure-related complications (in 3 patients in the ablation group and in 1 patient in the medical-therapy group), all of which were related to the vascular access site.

### PRIMARY END POINT AND ITS COMPONENTS

The median duration of follow-up was 18.0 months (interquartile range, 15.2 to 22.3) in the ablation group and 17.9 months (interquartile range, 14.2 to 22.3) in the medical-therapy group (overall population, 18.0 months; interquartile range, 14.6 to 22.6). A primary end-point event occurred in 8 patients (8%) in the ablation group and in 29 patients (30%) in the medical-therapy group (hazard ratio, 0.24; 95% confidence interval [CI], 0.11 to 0.52; P<0.001) (Fig. 1A and Table 2). Kaplan–Meier estimates of the cumulative incidence of primary end-point events at 1 and 2 years were 6% and 9%, respectively, in the ablation group and 28% and 31%, respectively, in the medical-therapy group.

Death from any cause occurred in 6 patients (6%) in the ablation group and in 19 patients (20%) in the medical-therapy group (hazard ratio, 0.29; 95% CI, 0.12 to 0.72) (Fig. 1B and Table 2). Kaplan–Meier estimates of 1-year and 2-year cumulative mortality were 4% and 6%, respectively, in the ablation group and 14% and 23%, respectively, in the medical-therapy group. Five of the deaths in the medical-therapy group occurred after implantation of a left ventricular assist device or after heart transplantation; except for one death in each group, all deaths were attrib-

**Table 3. Additional End Points.***

| End Point | Ablation Group | Medical-Therapy Group | Mean Between-Group Difference (95% CI)† |
|---|---|---|---|
| **Left ventricular ejection fraction** | | | |
| At baseline | | | |
| No. of patients evaluated | 97 | 97 | |
| Value — % | 29.0±6.4 | 27.7±6.3 | |
| At 6 mo | | | |
| No. of patients evaluated | 92 | 74 | |
| Baseline value — % | 29.4±6.2 | 28.7±5.9 | |
| Value at 6 mo — % | 36.2±8.7 | 29.9±7.1 | |
| Improvement — percentage points | 6.7±6.5 | 1.2±6.4 | 5.5 (3.5 to 7.5) |
| At 12 mo | | | |
| No. of patients evaluated | 92 | 70 | |
| Baseline value — % | 29.4±6.2 | 28.7±6.0 | |
| Value at 12 mo — % | 37.2±9.1 | 30.1±8.0 | |
| Improvement — percentage points | 7.8±7.6 | 1.4±7.2 | 6.4 (4.1 to 8.7) |
| **Atrial fibrillation burden** | | | |
| At baseline | | | |
| No. of patients evaluated | 97 | 97 | |
| Value — % | 50.2±31.9 | 49.3±34.4 | |
| At 6 mo | | | |
| No. of patients evaluated | 90 | 71 | |
| Baseline value — % | 50.8±31.0 | 50.7±34.7 | |
| Value at 6 mo — % | 20.0±28.3 | 42.4±35.2 | |
| Reduction — percentage points | 30.8±33.3 | 8.3±25.2 | 22.5 (13.1 to 31.9) |
| At 12 mo | | | |
| No. of patients evaluated | 89 | 66 | |
| Baseline value — % | 50.9±31.2 | 52.4±35.2 | |
| Value at 12 mo — % | 19.6±28.0 | 43.7±36.2 | |
| Reduction — percentage points | 31.4±33.3 | 8.6±26.3 | 22.7 (13.0 to 32.5) |

* Plus–minus values are means ±SD.
† Values were calculated with unpaired t-test methods that applied the changes at 6 and 12 months relative to baseline. Because the trial protocol did not include a provision for correction for multiplicity, results for secondary end points are reported as point estimates with 95% confidence intervals, without further statistical testing. The widths of the confidence intervals have not been adjusted for multiplicity, so they should not be used to infer definitive treatment effects for secondary end points.

utable to a cardiovascular cause. A left ventricular assist device was implanted in 1 patient (1%) in the ablation group and in 10 patients (10%) in the medical-therapy group (cause-specific hazard ratio, 0.09; 95% CI, 0.01 to 0.70) (Fig. 1C and Table 2). Urgent heart transplantation was performed in 1 patient (1%) in the ablation group and in 6 patients (6%) in the medical-therapy group (cause-specific hazard ratio, 0.15; 95% CI, 0.02 to 1.25) (Table 2). A subgroup analysis of the primary end point is provided in Table S5.

### OTHER END POINTS

The improvement in the left ventricular ejection fraction and the reduction in the atrial fibrillation burden are presented in Table 3 and Table

**Table 4. Atrial Fibrillation Classification and Amiodarone Use at 12 Months.**

| Variable | Ablation Group (N=97) | Medical-Therapy Group (N=97) |
|---|---|---|
| | *number (percent)* | |
| **Atrial fibrillation classification** | | |
| Baseline | | |
| Persistent | 69 (71) | 66 (68) |
| Paroxysmal | 28 (29) | 31 (32) |
| 12 mo | | |
| With primary end-point event | 8 (8) | 29 (30) |
| Without primary end-point event | 89 (92) | 68 (70) |
| Persistent | 35 (36) | 59 (61) |
| Paroxysmal | 49 (51) | 8 (8) |
| Sinus rhythm: no atrial fibrillation | 5 (5) | 1 (1) |
| **Amiodarone use** | | |
| Baseline: receiving amiodarone | 44 (45) | 46 (47) |
| 12 mo | | |
| With primary end-point event | 8 (8) | 29 (30) |
| Without primary end-point event | 89 (92) | 68 (70) |
| Receiving amiodarone | 28 (29) | 55 (57) |

S6. In the ablation group, the left ventricular ejection fraction improved by a mean (±SD) of 6.7±6.5 percentage points among 92 patients at 6 months and 7.8±7.6 percentage points among 92 patients at 12 months, as compared with 1.2±6.4 percentage points among 74 patients at 6 months and 1.4±7.2 percentage points among 70 patients at 12 months in the medical-therapy group (mean between-group difference, 5.5 percentage points [95% CI, 3.5 to 7.5] at 6 months and 6.4 percentage points [95% CI, 4.1 to 8.7] at 12 months). In the ablation group, the atrial fibrillation burden was reduced by a mean of 30.8±33.3 percentage points in 90 patients at 6 months and 31.4±33.3 percentage points in 89 patients at 12 months, as compared with reductions of 8.3±25.2 percentage points in 71 patients at 6 months and 8.6±26.3 percentage points in 66 patients at 12 months in the medical-therapy group (mean between-group difference, 22.5 percentage points [95% CI, 13.1 to 31.9] at 6 months and 22.7 percentage points [95% CI, 13.0 to 32.5] at 12 months). At 12 months, 54 of 97 patients (56%) in the ablation group were free of primary end-point events and not in persistent atrial fibrillation, as compared with 9 of 97 patients (9%) in the medical-therapy group. A total of 28 of 97 patients (29%) in the ablation group and 55 of 97 patients (57%) in the medical-therapy group were treated with amiodarone at 12 months (Table 4).

## DISCUSSION

In the CASTLE-HTx trial, we found that catheter ablation of atrial fibrillation plus medical therapy in patients with end-stage heart failure who were referred for transplantation evaluation was associated with a lower likelihood of a composite of death from any cause, implantation of a left ventricular assist device, or urgent heart transplantation than medical therapy alone. Fewer deaths from any cause and implantations of a left ventricular assist device occurred among the patients who received catheter ablation than among those who received medical therapy alone. There were few, minor adverse events related to catheter ablation.

Catheter ablation for patients with heart failure and atrial fibrillation has been shown to reduce arrhythmia burden, reverse left ventricular remodeling, and reduce mortality.[1-3,11-13] The role of catheter ablation for atrial fibrillation for patients with end-stage heart failure is unknown because these patients have been excluded from major trials.[1,3] Our trial suggests that in patients with atrial fibrillation and end-stage heart failure, catheter ablation may ameliorate the clinical course. Whether our findings are generalizable to patients with asymptomatic atrial fibrillation is unknown.[14,15] Differences in the occurrence of primary end-point events between the trial groups appeared to emerge early and be sustained during follow-up. However, consideration for catheter ablation should not postpone listing for transplantation.

It has become evident that arrhythmia burden is an important determinant of prognosis in patients with atrial fibrillation and heart failure.[1,13,16,17] It also seemed important to reduce arrhythmia burden through catheter ablation since antiarrhythmic drugs may reduce the arrhythmia burden but not improve clinical outcomes.[18-20] Catheter ablation appeared more likely to revert persistent to paroxysmal atrial fibrillation and prevent its progression than medical therapy (Table 4). A recent trial supports the benefit of catheter ablation over drug therapy for reducing the

burden of atrial fibrillation.[21] Appropriate timing of referral for consideration of catheter ablation may be challenging but may also result in less progression of heart failure, and the patient may still be amenable to interventions for advanced heart failure.[7,22,23]

Our trial has limitations. One limitation is that it was conducted at a single referral center. Another potential limitation is the early termination of the trial based on the recommendation of the data and safety monitoring board, and it is possible that the findings may have differed with longer-term follow-up. The open-label design might have influenced treatment decisions regarding the components of the primary end point. However, these decisions were made without knowledge of the patient's trial-group assignment during heart-team meetings. In addition, 16 patients in the medical-therapy group crossed over to undergo catheter ablation. However, because our analyses were reported on an intention-to-treat basis, this potentially may have decreased the treatment benefit associated with assignment to the ablation group.

In this trial involving patients with symptomatic atrial fibrillation and end-stage heart failure, catheter ablation plus medical therapy was associated with a lower likelihood of a composite of death from any cause, implantation of a left ventricular assist device, or urgent heart transplantation than medical therapy alone.

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

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

## APPENDIX

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