Circulation: Arrhythmia and Electrophysiology

ORIGINAL ARTICLE

# Catheter Ablation Versus Best Medical Therapy in Patients With Persistent Atrial Fibrillation and Congestive Heart Failure

## The Randomized AMICA Trial

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**BACKGROUND:** Optimal treatment of patients with persistent atrial fibrillation (AF) and heart failure (HF) with reduced left ventricular ejection fraction (LVEF) and an indication for internal defibrillator therapy is controversial.

**METHODS:** Patients with persistent/longstanding persistent AF and LVEF ≤35% were randomly allocated to catheter ablation of AF or best medical therapy (BMT). The primary study end point was the absolute increase in LVEF from baseline at 1 year. Secondary end points included 6-minute walk test, quality-of-life, and NT-proBNP (N-terminal pro-brain natriuretic peptide). Pulmonary vein isolation was the primary ablation approach; BMT comprised rate or rhythm control. All patients were discharged after index hospitalization with a cardioverter-defibrillator or cardiac resynchronization therapy defibrillator implanted. The study was terminated early for futility.

**RESULTS:** Of 140 patients (65±8 years, 126 [90%] men) available for the end point analysis, 68 and 72 patients were assigned to ablation and BMT, respectively. At 1 year, LVEF had increased in ablation patients by 8.8% (95% CI, 5.8%–11.9%) and in BMT patients by 7.3% (4.3%–10.3%; *P*=0.36). Sinus rhythm was recorded on 12-lead electrocardiograms at 1 year in 61/83 ablation patients (73.5%) and 42/84 BMT patients (50%). Device-recorded AF burden at 1 year was 0% or maximally 5% of the time in 28/39 ablation patients (72%) and 16/36 BMT patients (44%). There was no difference in secondary end point outcome between ablation patients and BMT patients.

**CONCLUSIONS:** The AMICA trial (Atrial Fibrillation Management in Congestive Heart Failure With Ablation) did not reveal any benefit of catheter ablation in patients with AF and advanced HF. This was mainly because of the fact that at 1 year, LVEF increased in ablation patients to a similar extent as in BMT patients. The effect of catheter ablation of AF in patients with HF may be affected by the extent of HF at baseline, with a rather limited ablation benefit in patients with seriously advanced HF.

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**VISUAL OVERVIEW:** A visual overview is available for this article.

**Key Words:** atrial fibrillation ■ catheter ablation ■ defibrillators ■ heart failure ■ randomized controlled trial



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### WHAT IS KNOWN?

- In patients with atrial fibrillation and heart failure, catheter ablation is superior to medical treatment.

### WHAT THE STUDY ADDS?

- The AMICA trial (Atrial Fibrillation Management in Congestive Heart Failure With Ablation) shows, in concordance with a subgroup analysis of the recent CASTLE-AF trial (Catheter Ablation Versus Standard Conventional Therapy in Patients With Left Ventricular Dysfunction and Atrial Fibrillation), that no benefit of catheter ablation and restoration of sinus rhythm is observed over best medical therapy in patients with persistent atrial fibrillation and heart failure with severely reduced left ventricular ejection fraction.

Congestive heart failure (HF) and atrial fibrillation (AF) often co-exist, where one condition promotes the development of the other.[1–5] A subgroup analysis in the AFFIRM trial (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) comparing patients in sinus rhythm (SR) with patients in AF highlighted the potential benefit of maintaining SR.[6] However, antiarrhythmic drugs have only a limited potential to maintain SR[7–9] and their negative effects may counterbalance the potential benefit of SR.

Observational studies of catheter ablation in patients without HF aiming at complete electrical isolation of the pulmonary veins (PVs)[10,11] could demonstrate that this ablation technique was able to restore stable SR in the majority of patients with persistent forms of AF unresponsive to electrical cardioversion.[12,13] The superiority of catheter ablation over antiarrhythmic drug therapy in these patients has been confirmed in randomized trials.[14–17] Additionally, 3 randomized controlled trials in patients with HF have also shown that catheter ablation was superior to antiarrhythmic medication as well as atrioventricular nodal ablation with pacemaker implantation.[18–20]

The AMICA trial (Atrial Fibrillation Management in Congestive Heart Failure With Ablation) was conceived as a randomized comparison of patients with persistent or longstanding persistent AF and a left ventricular ejection fraction (LVEF) ≤35% requiring implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy defibrillator (CRT-D) therapy; the patients were assigned to either catheter ablation of AF or best medical treatment (BMT). The objective of the study was to demonstrate the superiority of the catheter ablation strategy in terms of the absolute increase in LVEF from baseline to 1 year.

## METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

### Trial Design

AMICA was a multicenter, open-label, controlled, randomized trial. For the treatment of AF, patients were randomly assigned in a 1:1 ratio to one of 2 parallel groups, either drug therapy alone or catheter ablation in addition to drug therapy.

Study site selection was restricted to heart centers with a high expertise in the electrophysiological treatment of patients with AF.

The study was approved by local Ethics Committees, and written informed consent was obtained from each subject before performing any study procedure.

### Patient Selection

Patients aged 18 to 75 years presenting with a documented episode of symptomatic persistent or longstanding persistent AF and New York Heart Association class II or III HF were candidates for enrollment into the study. To fulfill the inclusion criteria, patients needed to have an indication for an ICD or a CRT-D, an LVEF of 35% or less and needed to be under optimal medical treatment for HF for at least 1 month. Persistent AF was defined to last for a minimum of 1 week to a maximum of 1 year and longstanding persistent AF for a minimum of 1 year to a maximum of 4 years. Patients with a left atrial diameter of >60 mm in parasternal axis, an underlying valvular heart disease (without correction) and previous PV isolation procedures were excluded from the study (Table I in the Data Supplement).

### Randomization

Randomization was done in a 1:1 ratio through a web-based application using computer-generated lists of random numbers in a block design, stratified by device type (ICD or CRT-D), severity of AF (persistent or longstanding persistent), and study site.

### Echocardiography

Echocardiograms were centrally assessed at an echocardiography core laboratory (West German Heart Center, Essen, Germany). LVEF assessment was originally intended to use contrast echocardiography. However, as the contrast agent became commercially unavailable in Europe, all patients underwent standardized 2-dimensional noncontrast transthoracic echocardiographic imaging at baseline, discharge, and 12 months. LVEF was determined according to Simpson rule from left ventricular end-diastolic and end-systolic volumes in apical 5- and 2-chamber views. To determine LVEF during SR and AF, 3 and 5 to 10 beats were averaged, respectively.

### Treatment

In patients randomized to catheter ablation, a circumferential PV isolation was mandatory as primary method. Additional ablation techniques including the creation of linear lesions, ablation of complex fractionated atrial electrograms, or combinations thereof were left to the discretion of the investigator for a secondary ablative approach. The acute end point of AF ablation was the creation of bidirectional conduction block in all PVs. Mapping should be

performed with the Ensite Precision 3D cardiac mapping system (St Jude Medical, Inc, Saint Paul, MN).

BMT conformed to the American College of Cardiology/American Heart Association/European Society of Cardiology 2006 Practice Guidelines for the Management of Patients with AF[21] regardless of whether a rate or rhythm control strategy was selected. If applicable, patients were placed on an antiarrhythmic drug and, if necessary, cardioverted to SR.

If not implanted at the time of enrolment, patients received an ICD or CRT-D, such that all patients were discharged after the index hospitalization with either device in place.

All therapies were established and optimized in a 90-day treatment initiation phase (blanking period) starting with randomization. During this time, patients could receive alternative drugs, electrical cardioversion or undergo repeat ablation (AF ablation group). HF drug therapy could also be optimized. Ablation-group patients could be maintained on antiarrhythmic drug until the end of the blanking period.

Follow-up visits were scheduled at 1, 3 (end of blanking period), 6, and 12 months.

## Objectives/End Points

The primary study end point was the absolute increase in LVEF from baseline to 1 year after randomization.

Secondary end points included 6-minute walk distance, self-assessed quality-of-life, BNP (brain natriuretic peptide or NT-proBNP [N-terminal pro-brain natriuretic peptide]) levels, AF burden, adverse events, and mortality. Quality-of-life was assessed using Minnesota living with HF questionnaire total score of 21 questions with answers graded from 0 (no effect on HF/condition) to 5 (strong effect on HF/condition).

Heart rhythm was assessed by 12-lead ECG recording at follow-up visits and by patient-performed surface recordings. At discharge, the patients were instructed to record their heart rhythm for 30 seconds daily and, in case of symptoms, with an external noninvasive device (Vitaphone ECG-Monitoring-Card VP 100ir). ECG recordings were transmitted via telephone to the Vitaphone TeleMedical Service Center. AF burden was collected from ICD/CRT-D device memory. For reasons of conformity, only data from St Jude Medical manufactured devices were included in the analysis.

## Statistics

Continuous variables are described by mean ± SD as well as by median and interquartile range. Differences between treatment groups in continuous variables were assessed by ANCOVA for the primary end point, that is, the change in LVEF from baseline to month 12, and by mixed-effect model repeat measurement for the secondary variables BNP, NT-proBNP, 6-minute walk distance, and Minnesota living with HF questionnaire total score.

Categorical variables are described with absolute and relative frequencies. The proportion of patients with SR was analyzed using a logistic regression model, including treatment group, device type, type of AF, SR at baseline, visit, and treatment-by-visit interaction as effects. A similar logistic regression analysis was done for the proportion of patients with total time in atrial tachycardia or AF of at most 5%. Differences between treatment groups in adverse event rates were evaluated with the $\chi^2$ test or Fisher exact test. Event-free survival was assessed with Kaplan-Meier estimates, and treatment groups were compared with the log-rank test. All statistical tests and resulting *P* values, except for the primary end point, are exploratory.

The primary study end point was analyzed using a mixed model ANCOVA with treatment group, device type (ICD implant, CRT-D preimplanted, CRT-D newly implanted) at hospital discharge, and type of AF (persistent or longstanding persistent) as fixed effects, center as random effect, and baseline LVEF as continuous covariate.

Four sensitivity analyses of the primary end point were performed. (1) Using a regression-based multiple imputation method for missing LVEF values (separately for each treatment group) and analyzing the multiply imputed dataset with the mixed model ANCOVA mentioned above; (2) using mixed-effect model repeat measurement for the LVEF change from baseline to hospital discharge and to 1 year; (3) using local transthoracic echocardiographic data in cases of missing central transthoracic echocardiographic data; and (4) using the per-protocol patient set, which excluded all patients with major protocol violations.

It was hypothesized that BMT was associated with a 5% absolute increase in LVEF at 1 year, as opposed to a 15% absolute increase in LVEF following catheter ablation.[22] The sample size was calculated to provide 90% power to detect a difference of 10% between the 2 study groups (assuming a common SD of 20%) with a 2-sided unpaired *t* test and 5% significance level. The required sample size was 172; assuming a drop-out rate of 20%, the final sample size was set at 216 patients (108 per group).

All statistical analyses of study data were performed using the SAS software, version 9.4.

# RESULTS

## Patients

Between January 2008 and June 2016, 202 patients were enrolled at 17 study sites in Germany, Hungary, and Spain (Table II in the Data Supplement). Patient follow-up was completed in July 2017. Enrollment was prematurely terminated by the Steering Committee for futility on recommendation of the Data Safety Monitoring Board following a second, not prespecified interim analysis. The decision was not related to any safety concerns. After stopping enrollment, follow-up was continued for each active patient until regular study termination at 12 months. The mean duration of follow-up was 358±71 days (median 368 days). Randomization had assigned 104 patients to catheter ablation of AF and 98 patients to BMT (Figure 1). Seven patients (4 in the ablation group, 3 in the BMT group) were excluded from the study after randomization and before any further intervention due to violation of inclusion criteria (n=5) or on patient request (n=2), leaving 100 ablation-group patients and 95 BMT group patients as the full analysis set for safety and efficacy end points. However, with 17 patients in the ablation group and 13 patients on BMT terminating the study before the 1-year follow-

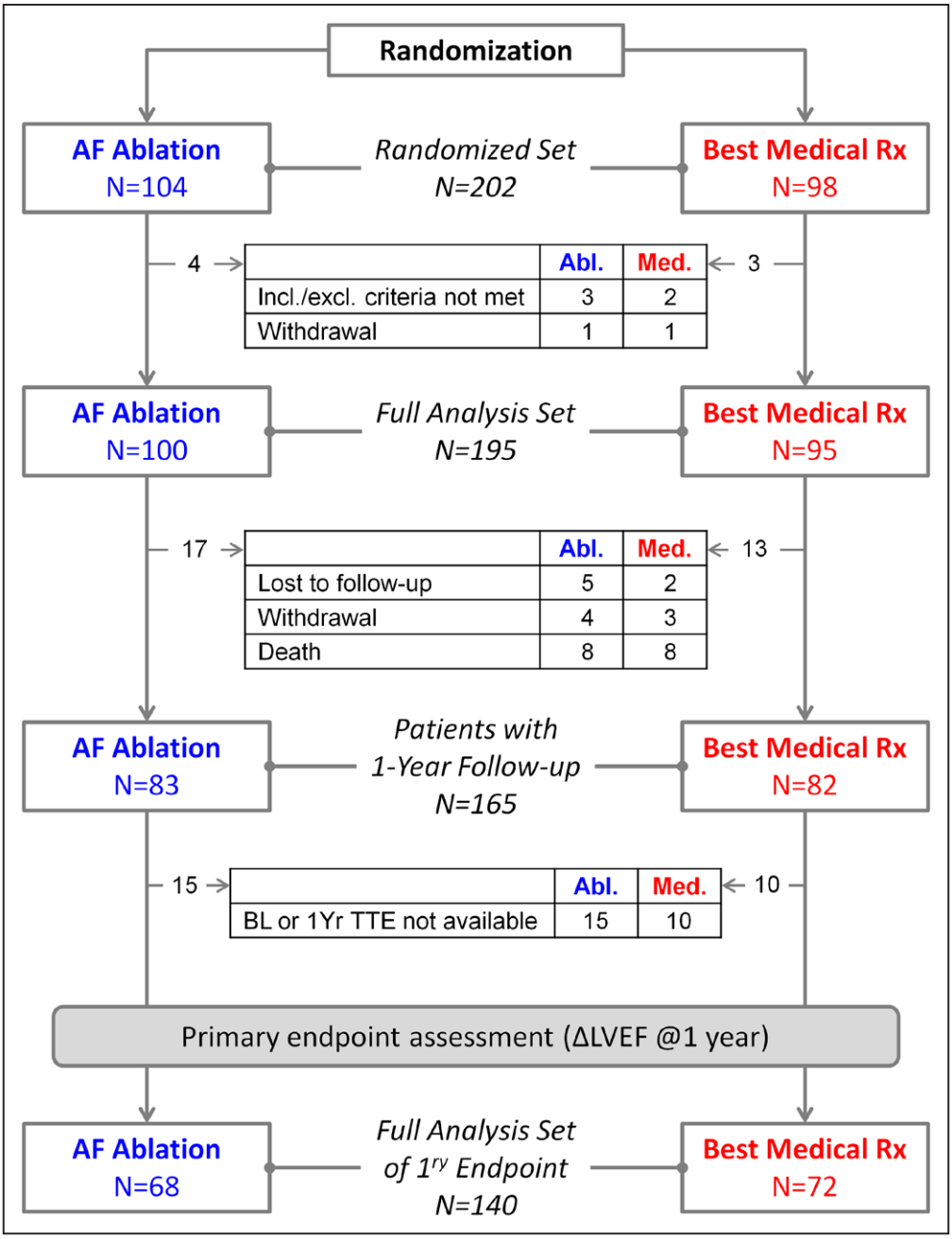



**Figure 1. Flowchart of randomized and analyzed patients.**
Of the 202 patients enrolled, 104 were randomized to catheter ablation and 98 to best medical therapy. The primary efficacy end point analysis (assessment of the change [Δ] in left ventricular ejection fraction [LVEF] from baseline to 1 y) was performed in 68 and 72 patients, respectively. AF indicates atrial fibrillation; BL, baseline; Rx, therapy; and TTE, transthoracic echocardiography.



up visit (16 because of death, 8 in each group), and 25 patients (15 in the ablation group and 10 on BMT) whose echocardiograms were not analyzable at baseline or 1 year, a total of 140 patients were included in the primary efficacy end point analysis, 68 patients (65%) from the ablation group and 72 (73%) from the BMT group (Figure 1). Data for the full analysis set of the primary end point are presented in this article unless otherwise indicated.

The patients' baseline characteristics are shown in Table 1. Mean patient age was 65 years, overall 90% were men, and all patients had persistent AF. Long-standing persistent AF was present in 19% of patients assigned to catheter ablation and 28% of patients assigned to BMT. In both treatment groups, about 60% had New York Heart Association class III HF symptoms. Implanted device types are shown in Tables 1 and 2 (for patients of the full analysis set see Tables III and IV in the Data Supplement).

The patients' medication at baseline, 6, and 12 months is shown in Table 3 (for patients of the full analysis set see Table V in the Data Supplement).

**Table 1. Baseline Characteristics of Patients Entered in the Primary Efficacy End Point Analysis**

| | Ablation (N=68) | Best Medical Therapy (N=72) |
|---|---|---|
| Age, y | 65±8; 66 [59–72] | 65±8; 65 [59–71] |
| Men | 60 (88) | 66 (92) |
| Body mass index, kg/m$^2$ | 29.4±5.0; 29.4 [26.2–32.7] | 28.4±4.5; 27.5 [25.2–31.2] |
| NYHA functional class | | |
| II | 28 (41) | 27 (38) |
| III | 40 (59) | 45 (62) |
| Cause of heart failure | | |
| Ischemic cardiomyopathy | 30 (44) | 40 (56) |
| Nonischemic cardiomyopathy | 38 (56) | 32 (44) |
| Coexisting conditions | | |
| Diabetes mellitus | 24 (35) | 22 (31) |
| Arterial hypertension | 56 (82) | 55 (76) |
| Chronic renal insufficiency | 20 (29) | 25 (35) |
| Type of atrial fibrillation | | |
| Persistent | 55 (81) | 52 (72) |
| Longstanding persistent | 13 (19) | 20 (28) |
| LV ejection fraction, % | 27.8±9.5; 27.6 [20.4–34.0] | 24.8±8.8; 24.8 [18.0–30.0] |
| Left atrial diameter, mm | 50±6; 50 [46–55] | 51±5; 51 [48–55] |
| LV end-diastolic volume, mL | 196±70; 185 [150–219] | 192±63; 175 [152–209] |
| LV end-systolic volume, mL | 143±60; 134 [104–173] | 147±59; 135 [105–170] |
| No. of DCCVs in previous 2 y | | |
| 0 | 23 (34) | 18 (25) |
| 1 | 9 (13) | 13 (18) |
| ≥2 | 5 (7) | 4 (6) |
| unknown | 31 (46) | 37 (51) |
| Defibrillator implant status at enrolment | | |
| None | 33 (49) | 37 (51) |
| ICD | 18 (27) | 19 (26) |
| CRT-D | 17 (25) | 16 (22) |
| Heart rate, min$^{-1}$ | 82±22; 79 [69–96] | 86±22; 80 [70–100] |
| Rhythm | | |
| Sinus rhythm | 9 (13) | 4 (6) |
| Atrial fibrillation | 56 (82) | 66 (92) |
| Atrial flutter | 1 (1) | 1 (1) |
| Atrial tachycardia | 2 (3) | 1 (1) |
| Other | 0 (0) | 1 (1) |

Values are mean±SD, median [first–third quartile] or n (%). CRT-D indicates cardiac resynchronization therapy defibrillator; DCCV, direct current cardioversion; ICD, implantable cardioverter-defibrillator; LV, left ventricular; and NYHA, New York Heart Association.

**Table 2. Index Procedural and Discharge Characteristics of Patients Entered in the Primary Efficacy End Point Analysis**

| | Ablation (N=68) | Best Medical Therapy (N=72) |
|---|---|---|
| Procedure | | |
| New implantation of ICD | 21 (31) | 20 (28) |
| New implantation of CRT-D | 12 (18) | 17 (24) |
| Catheter ablation of AF performed | 67 (99) | 0 (0) |
| Primary mode of ablation | | |
| Pulmonary vein isolation | 67/67 (100) | … |
| Secondary mode of ablation | | |
| Additional linear lesions | 22/67 (33) | … |
| CFAE ablation | 7/67 (10) | … |
| Combination/other | 4/67 (6) | … |
| Procedure duration,* min | 157±47; 150 [120–190] | … |
| Procedural outcome | | |
| Success | 67/67 (100) | … |
| Confirmed success | 65/67 (97) | … |
| DCCV | | |
| During ablation procedure | 45/67 (67) | … |
| Before discharge | 7/67 (10) | 38/71 (54) |
| Discharge | | |
| Patients with ICD | 39 (57) | 39 (54) |
| Single chamber | 13 (19) | 14 (19) |
| Dual chamber | 26 (38) | 25 (35) |
| Patients with CRT-D | 29 (43) | 33 (46) |
| Patients on amiodarone | 27 (40) | 46/71 (65) |

Values are mean±SD, median [range], n/N (%), or n (%). AF indicates atrial fibrillation; CFAE, complex fractionated atrial electrogram; CRT-D, cardiac resynchronization therapy defibrillator; DCCV, direct current cardioversion; and ICD, implantable cardioverter-defibrillator.

*From groin puncture to sheath removal.

In the course of this study, 3/72 patients in the BMT group (4%) crossed over to AF ablation between months 4 and 9 after randomization, and 1/68 patient (1.5%) did not undergo AF ablation despite randomization.

PV isolation was performed in 67/68 patients (99%), whereas 1 patient underwent AV nodal ablation rather than AF ablation because of renal failure. Additional AF ablation was performed in a total of 33 patients (49%; Table 2). Circumferential ablation of all PVs was completed in all 67 patients (100%); acute procedural success was confirmed by bidirectional block in 65/67 patients (97%).

A repeat ablation attempt for AF recurrence was performed in 10/67 patients (15%); 2 patients underwent 2 repeat ablation procedures.

The use of amiodarone over time is illustrated in Figure 2.

## Primary Efficacy End Point

The least-squares mean absolute increase in LVEF from baseline to 1 year was 8.8% (95% CI, 5.8%–11.9%)

**Table 3. Medication Across Study Visits of Patients Entered in the Primary Efficacy End Point Analysis**

| | Ablation | | | Best Medical Therapy | | |
|---|---|---|---|---|---|---|
| | Baseline (n=68) | 6 mo (n=67) | 12 mo (n=68) | Baseline (n=72) | 6 mo (n=71) | 12 mo (n=72) |
| β-Blocker | 62 (91) | 62 (93) | 65 (96) | 67 (93) | 68 (96) | 69 (96) |
| ACE inhibitor or ARB | 62 (91) | 62 (93) | 61 (90) | 68 (94) | 66 (93) | 70 (97) |
| Anticoagulant | 54 (79) | 55 (82) | 56 (82) | 61 (85) | 68 (96) | 66 (92) |
| Diuretic | 60 (88) | 60 (90) | 59 (87) | 60 (83) | 60 (85) | 63 (88) |
| Aldosterone antagonist | 44 (65) | 50 (75) | 49 (72) | 48 (67) | 54 (76) | 52 (72) |
| Statin | 43 (63) | 47 (70) | 49 (72) | 40 (56) | 44 (62) | 48 (67) |
| Antiplatelet | 24 (35) | 16 (24) | 11 (16) | 26 (36) | 23 (32) | 20 (28) |
| Digitalis | 20 (29) | 12 (18) | 11 (16) | 21 (29) | 24 (34) | 20 (28) |
| Amiodarone | 17 (25) | 23 (34) | 23 (34) | 27 (38) | 40 (56) | 39 (54) |

ACE indicates angiotensin-converting enzyme; and ARB, angiotensin II receptor blocker.

in the ablation group and 7.3% (4.3%–10.3%, *P*=0.36) in the BMT group, indicating that both treatment groups improved in essentially the same way over 1 year.

The variation in LVEF over time is shown in Figure 3 for both treatment groups. Note near parallel course of LVEF over time in either group.

Sensitivity and subgroup analyses confirmed the above findings. Treatment differences in the 4 sensitivity analyses of the primary end point ranged from 0.11% to 1.23% (with *P* values between 0.46 and 0.95) in favor of AF ablation and were thus even lower than the 1.5% difference in LVEF increase seen in the primary analysis. A subgroup analysis of the primary end point by type of defibrillator implant (ICD versus preimplanted CRT-D versus newly implanted CRT-D) yielded best results in favor of AF ablation in patients with a preimplanted CRT-D (17 AF ablation, 16 BMT); however, the difference of 5.1% was not statistically significant. A further subgroup analysis of dichotomizing the baseline LVEF (≤26.1% [median] versus >26.1%) did also not reveal a relevant treatment group difference in LVEF increase.

## Secondary End Points

Data presented for the secondary end points are from the full analysis set (N=195).

## Rhythm Control

Following catheter ablation, SR was found on 12-lead ECGs in 79% of patients at discharge and 73% at 3 months; the latter prevalence was essentially maintained throughout the remaining follow-up, with 61/83 (73.5%) of ablation-group patients in SR at 1 year (Figure 4A). Of patients assigned to BMT, 52% were in SR at hospital discharge, a rate that had slightly dropped to 46% at 3 months and slightly risen again to 50% (42/84 patients) at 1 year (Figure 4A).

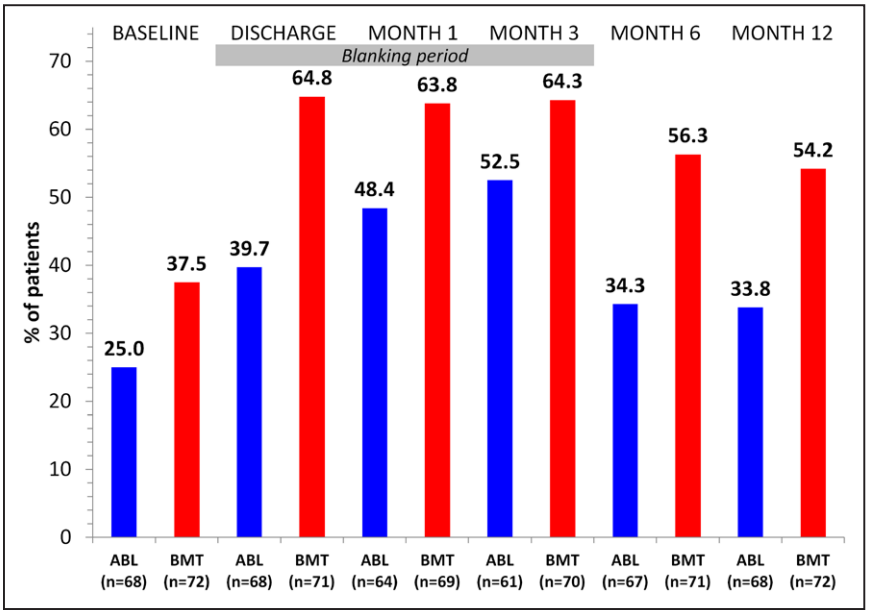
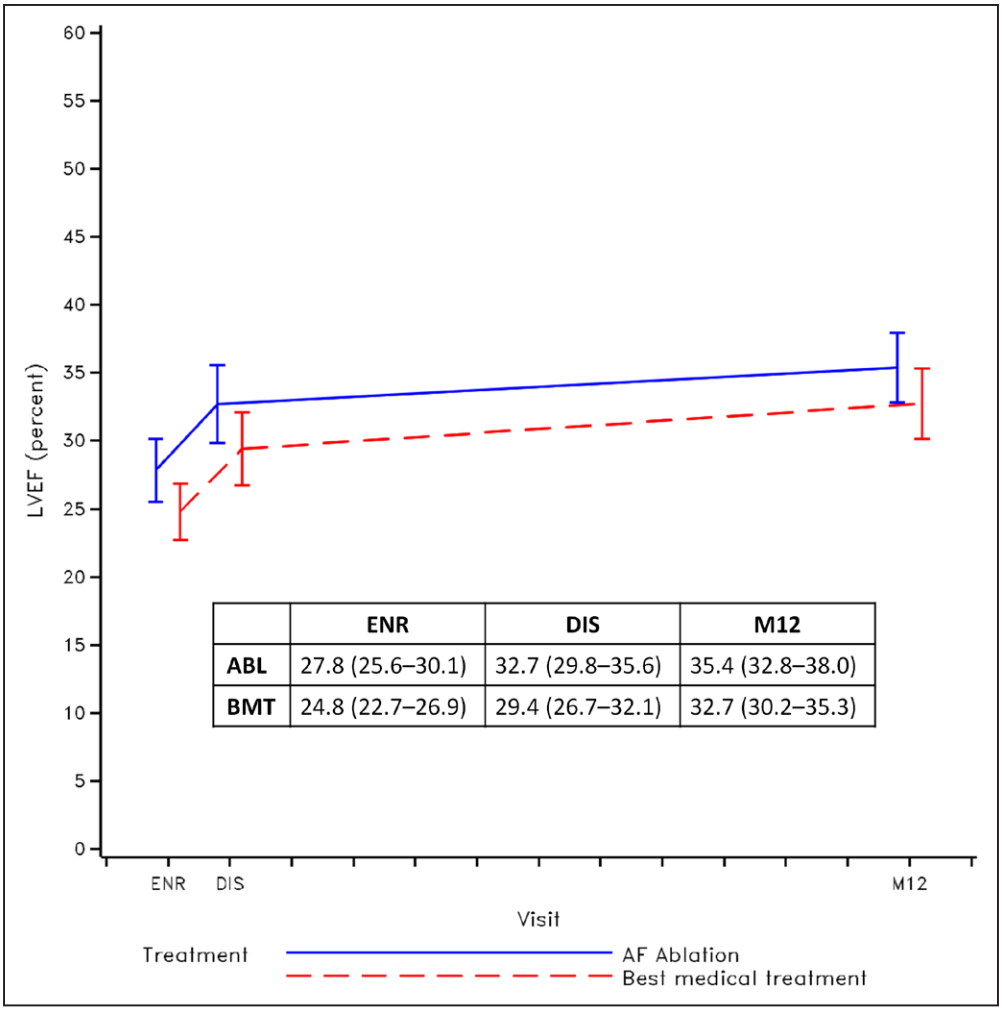



**Figure 2. Use of amiodarone over time in patients included in the primary efficacy end point analysis.**
At 1 y, 33.8% of patients in the ablation (ABL) group and 54.2% of patients in the best medical therapy (BMT) group were taking amiodarone.




| | ENR | DIS | M12 |
|---|---|---|---|
| ABL | 27.8 (25.6–30.1) | 32.7 (29.8–35.6) | 35.4 (32.8–38.0) |
| BMT | 24.8 (22.7–26.9) | 29.4 (26.7–32.1) | 32.7 (30.2–35.3) |

**Figure 3. Left ventricular ejection fraction (LVEF) over time.**
Shown are raw means with 95% CI. AF indicates atrial fibrillation; DIS, discharge; ENR, enrollment; and M12, month 12.

## Atrial Tachycardia/AF Burden

The atrial tachycardia/AF burden, that is, the total percent of time spent in high atrial rates (atrial tachycardia or AF) as recorded during follow-up in patients implanted with a dual-chamber ICD or a CRT-D device, is illustrated in Figure 4B. At 1 year, data from 39 ablation-group patients and 36 BMT group patients were available. A cumulative 72% of the former, as opposed to 44% of the latter, experienced either no high atrial rates at all (23% and 28%, respectively) or for maximally 5% of the time (49% and 17%, respectively).

## Six-Minute Walk Test, Quality-of-Life, BNP

The mean increase in 6-minute walk distance (+46 m in ablation patients, +81 m in BMT patients, *P*=0.07), the mean decrease in the total Minnesota living with HF questionnaire quality-of-life score (–11.2 and –8.9, respectively, *P*=0.42), and the median decrease in NT-proBNP levels (–891 and –419 pg/mL, respectively, *P*=0.60) were statistically not different between the treatment groups (Figure 5).

## Safety

Safety aspects were assessed in the full analysis set of 195 patients according to the patient's actual exposure to treatment at the time of the event. Five of the 100 patients in the ablation group did not receive AF ablation and consequently, safety in these was analyzed for BMT (N=100). The safety analysis for the ablation group (N=98) comprised 95 patients who had been exposed to the randomized ablation plus 3 crossover patients of the BMT group from time of ablation; (Table 4). In both treatment groups, 8 patients died during follow-up. Sixty-four ablation-group patients (65.3%) and 56 BMT group patients (56.0%; *P*=0.19) experienced at least 1 serious adverse event. Serious adverse events related to the ablation procedure (including atrioesophageal fistula leading to death [n=1], cardiogenic shock [n=1], pericardial tamponade

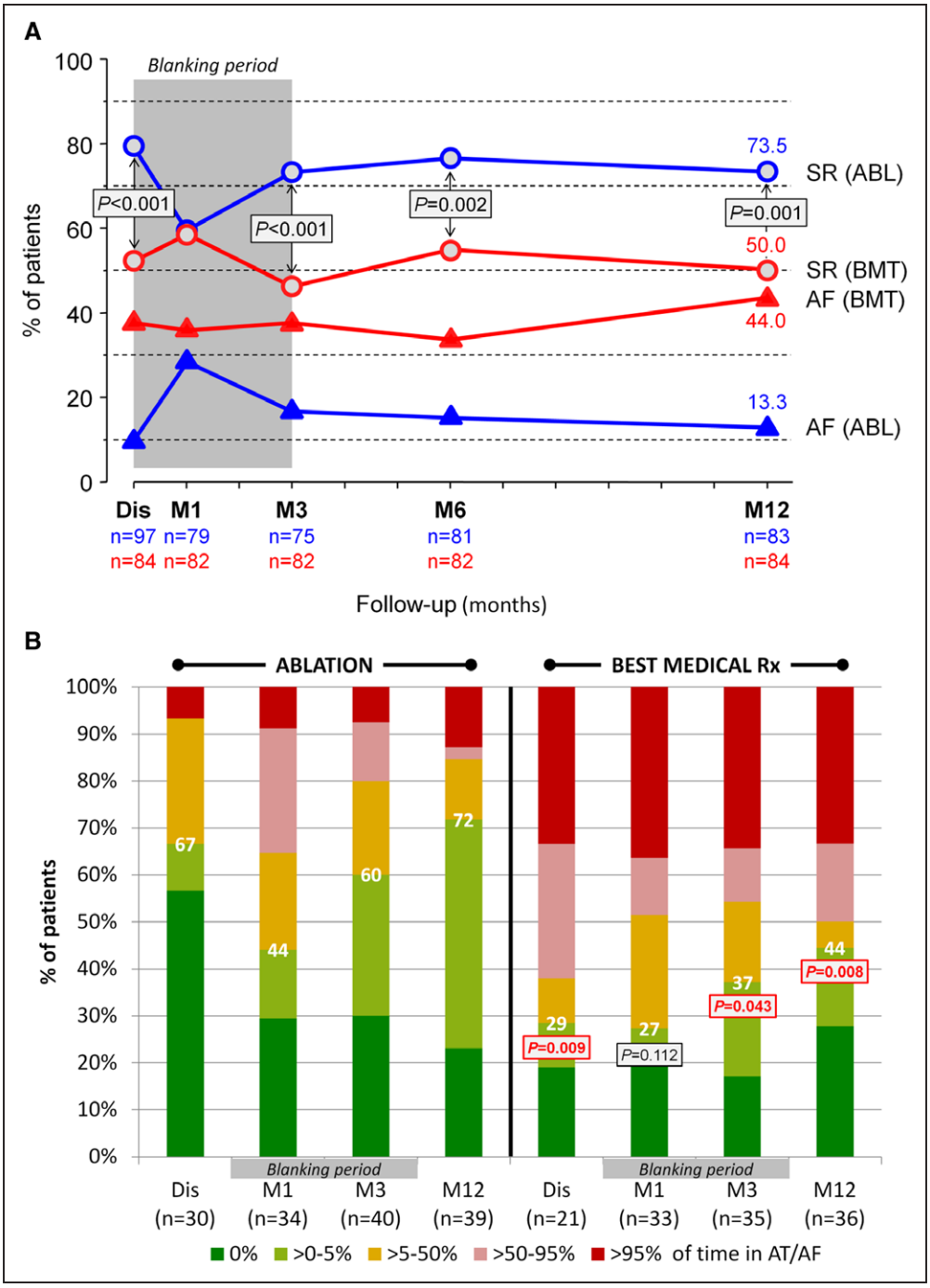



**Figure 4. Rhythm control and atrial tachycardia/fibrillation burden throughout follow-up.**
**A**, Rhythm control (from 12-lead electrocardiograms) over time in patients included in the full analysis set. At 1 y, 73.5% of patients in the ablation (ABL) group and 50.0% of patients in the best medical therapy (BMT) group were in sinus rhythm (SR; circles). Corresponding rates of SR in the full analysis set of the primary end point were 75.0% and 51.4%. Triangles denote percent of patients of either group in atrial fibrillation (AF). The *P* values were derived from a logistic regression model, including treatment group, device type, type of AF, SR at baseline, visit, and treatment-by-visit interaction as effects. **B**, Atrial tachycardia (AT)/AF burden over time in patients in the full analysis set with implantable devices capable of recording arrhythmic events. Stacked columns show percent of patients by time-spent-in-AT/AF categories. Numbers in stacked columns denote percent of patients who were maximally 5% of the time in AT/AF. The indicated burden refers to the time since last visit. At 1 y, that was the case in 72% of ablation-group patients and 44% of patients in the BMT group. The *P* values were derived from a logistic regression model, including treatment group, device type, type of AF, visit, and treatment-by-visit interaction as effects. Dis indicates discharge; and M, month.

[n=1], pleural effusion [n=1], suspected pericarditis [1], damage of ICD system [n=1], and vascular access complications [n=2]) were observed in 6 patients. Of note, there were no statistically significant differences between groups in the incidence (8.2% and 8.0%, respectively) and type of death (*P*=0.26) or in the incidence of serious cardiac disorders (48% and 43%, respectively; *P*=0.57; Table 4).

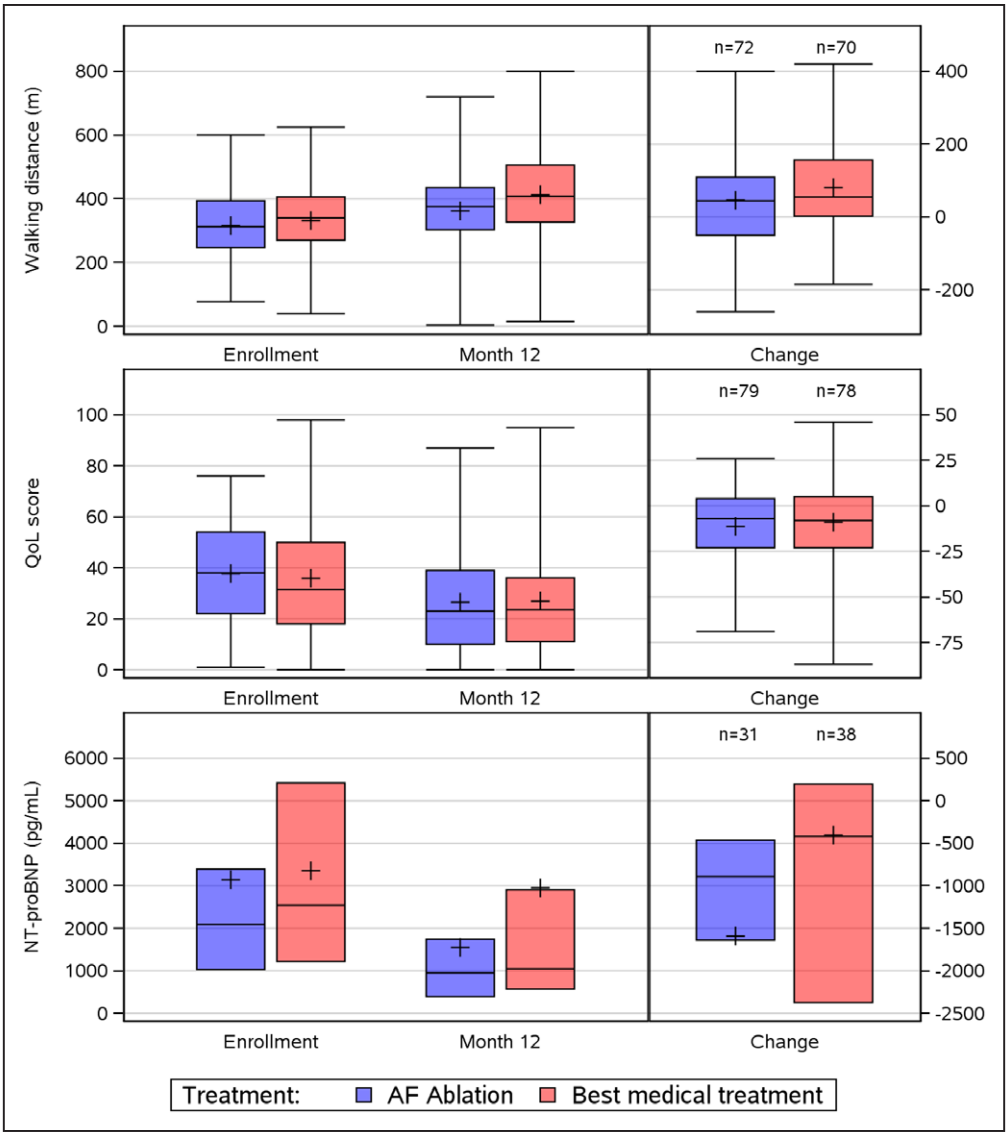



**Figure 5. Box-and-whiskers plots of secondary end points at baseline and 1 y and of change from baseline to 1 y.**
Top and bottom of box denote 75th and 25th percentile, respectively; horizontal line in box denotes median; plus sign in box denotes mean; top and bottom end of whiskers denote maximum and minimum, respectively. **Top**, Six-minute walk distance. *P*=0.07 for change. **Middle**, Minnesota living with heart failure questionnaire quality-of-life (QoL) score. *P*=0.42 for change. **Bottom**, NT-proBNP (N-terminal pro-brain natriuretic peptide). *P*=0.60 for change. Due to extreme outliers, no whiskers are presented for NT-proBNP.

## DISCUSSION

The AMICA trial comparing catheter ablation and BMT in patients with persistent forms of AF and advanced HF with significantly reduced LVEF had the following main results.

LVEF increased from baseline to 1 year by 8.8% in the ablation group, but also by 7.3% in the BMT group, indicating that both treatment groups improved in essentially the same way over 1 year.

At 1 year, ablation-group patients spent significantly more time in SR than BMT group patients, as documented by ICD storage and 12-lead ECG.

No statistically significant differences between treatment groups were observed in the secondary end points of change in 6-minute walk distance, change in quality-of-life score, and change in NT-proBNP level.

The AMICA trial thus confirmed that catheter ablation of AF has the potential to increase LVEF as shown in previous trials.[18–20] The absolute increase at 1 year of 8.8% was lower than expected from the literature and lower than the 15% hypothesized in the trial. However, in contrast to other trials, the LVEF in the AMICA control group also improved by 7.3%, which was higher than expected from the literature and higher than the hypothesized 5% increase. Therefore, AMICA must be considered a negative trial, with no between-group difference in the primary end point. This conclusion is supported by all secondary end points, which also did not show any difference between the ablation and the BMT group.

**Table 4. Adverse Events**

| | Ablation (N=98) | Best Medical Therapy (N=100) | *P* Value |
|---|---|---|---|
| Patients with ≥1 serious adverse event | 64 (65.3) | 56 (56.0) | 0.19 |
| Death | | | 0.26 |
| Cardiac | 3 (3.1) | 6 (6.0) | |
| Noncardiac | 3 (3.1) | 0 (0.0) | |
| Unknown | 2 (2.0) | 2 (2.0) | |
| Serious adverse events | | | |
| Cardiac disorder | 47 (48.0) | 43 (43.0) | 0.57 |
| Atrial arrhythmia | 27 (27.6) | 18 (18.0) | 0.13 |
| Worsening of heart failure | 15 (15.3) | 21 (21.0) | 0.36 |
| ICD system related | 8 (8.2) | 7 (7.0) | 0.79 |
| Ventricular arrhythmia | 4 (4.1) | 2 (2.0) | 0.44 |
| Other | 3 (3.1) | 6 (6.0) | 0.50 |
| Coronary artery disease related | 2 (2.0) | 4 (4.0) | 0.68 |
| Valvular | 2 (2.0) | 1 (1.0) | 0.62 |
| Vascular disorder | 6 (6.1) | 3 (3.0) | 0.33 |
| Noncardiovascular disorders | 32 (32.7) | 28 (28.0) | 0.54 |

Values are n (%). In case of treatment crossover from best medical therapy to AF Ablation, patients were analyzed for both treatments according to their exposure. AF indicates atrial fibrillation; and ICD, implantable cardioverter-defibrillator.

It appears reasonable to speculate on why AMICA is a negative trial, whereas CASTLE-AF (Catheter Ablation Versus Standard Conventional Therapy in Patients With Left Ventricular Dysfunction and Atrial Fibrillation[19]) came out positive. CASTLE-AF had a composite primary clinical end point, namely, death and hospitalization for worsening HF, whereas AMICA had a surrogate primary end point, namely, improvement in LV ejection fraction. Interestingly, in CASTLE-AF most of the benefits gained by catheter ablation were seen after 12 months during the second and third year of follow-up.[19] As the structured follow-up in AMICA ended after 12 months it seems possible that longer follow-up duration may be necessary in severe HF patients to detect the effects of interventions. However, as has been shown in many trials,[23–25] a reduction in the incidence of all-cause mortality and HF hospitalization is caused by reverse remodeling, which improves left ventricular function (ie, increases LVEF) via the reduction of LV end-systolic and end-diastolic volumes. The 1-year increase in LVEF following catheter ablation was nearly the same in AMICA at 8.8% and CASTLE-AF at 7.0%. It was also similar to the 1-year increase in LVEF of 9.6% observed in AATAC-AF (Ablation Versus Amiodarone for Treatment of Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted ICD/CRTD[18]), another positive, randomized ablation versus drug trial in AF patients with HF.

However, in AMICA, left ventricular function improved to a similar degree in the control group as in the ablation group, whereas the control groups of CASTLE-AF and AATAC-AF improved only by 2.0% and 4.2%, respectively. In other words, the AMICA trial was not negative due to the lack of a treatment effect in the ablation arm but due to a similar effect in the control arm. This finding is surprising since all patients enrolled in AMICA were on optimal HF treatment at the time of randomization; however, it is supported by a similarly contradictory observation in 2 recent trials of HF patients with mitral regurgitation randomized to MitraClip (treatment) or no MitraClip implantation (control) in addition to optimal medical therapy.

The COAPT trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation[26]) was a positive trial, with a highly significant treatment-related reduction in the composite clinical end point of total mortality and HF hospitalization, whereas MITRA-FR (Multicenter Study of Percutaneous Mitral Valve Repair with the MitraClip Device in Patients with Severe Secondary Mitral Regurgitation[27]) was negative for the same primary end point. Control patients in MITRA-FR ended up with a 10% higher event rate for the primary end point than did control patients in COAPT.

In AMICA, one explanation of the lack in LVEF increase beyond the documented 8%—despite the higher prevalence of SR in the ablation group than in the BMT group—might be that the overall patient population enrolled in AMICA was too sick to benefit from AF ablation and restoration of SR. Indeed, a direct comparison of the patient demographics in AMICA versus CASTLE-AF shows that AMICA included a sicker patient population with more advanced HF symptoms. At baseline, ablation patients in AMICA had a lower median LVEF (27.6% versus 32.5% in CASTLE-AF), had a higher prevalence of persistent or longstanding persistent AF (100% versus 70%), had more often HF symptoms of New York Heart Association functional classes III or IV (60% versus 31%), and had more often a cardiac resynchronization therapy defibrillator implanted (43% versus 27%) indicating left bundle branch block.

Thus, AMICA may indicate that not all patients with AF and HF will profit from an AF ablation procedure despite restoration of SR. One may speculate that patients with less advanced HF and a better LVEF—as those in CASTLE-AF—may derive more clinical benefit from restoration of SR than patients with more advanced HF. This is supported by subgroup analyses of the primary end point in CASTLE-AF, in which patients with New York Heart Association functional class III HF symptoms as well as patients with an LVEF <25% showed no benefit of catheter ablation.

Patients who underwent catheter ablation did not have more adverse effects than patients in the control

arm. In particular, the ablation procedure was relatively safe considering that all patients had advanced HF and a poor LV function. Ablation-specific serious complications, including 1 death, occurred in 6 patients. One patient died from an atrioesophageal fistula, which is a rare but almost always fatal complication,[28,29] and another sustained a cardiac tamponade, which is the most common AF ablation-related serious complication.[30,31]

## Limitations

This study was prematurely terminated for futility. Therefore, the projected patient number was not reached. Furthermore, 12% of patients could not be assessed for the primary end point due to nonanalyzable or missing echocardiographic studies. This further reduced the number of patients in relation to the projected number of patients required to test the study hypothesis. In addition, the increase in LVEF in the ablation arm was lower than projected. Therefore, more patients would have been necessary to adequately address the study hypothesis.

## Conclusions

The AMICA trial did not reveal any benefit of catheter ablation in patients with AF and advanced HF with significantly reduced LVEF. This was mainly due to the fact that at 1 year, LVEF had increased in ablation patients to a similar extent as in BMT patients, despite the fact that at any time during follow-up, ablation-group patients had more often SR on their surface ECG and a lower AF burden than BMT patients. It is concluded that the effect of catheter ablation of AF in HF patients may be affected by the extent of HF at baseline, with a rather limited ablation benefit in patients with seriously advanced HF.

## ARTICLE INFORMATION

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