Circulation

ORIGINAL RESEARCH ARTICLE

Ablation Versus Drug Therapy for Atrial Fibrillation in Heart Failure

Results From the CABANA Trial

Editorial, see p 1391

Douglas L. Packer, MD
Jonathan P. Piccini, MD
Kristi H. Monahan, RN
Hussein R. Al-Khalidi, PhD
Adam P. Silverstein, MS
Peter A. Noseworthy, MD
Jeanne E. Poole, MD
Tristram D. Bahnson, MD
Kerry L. Lee, PhD
Daniel B. Mark, MD
For the CABANA Investigators

BACKGROUND: In patients with heart failure and atrial fibrillation (AF), several clinical trials have reported improved outcomes, including freedom from AF recurrence, quality of life, and survival, with catheter ablation. This article describes the treatment-related outcomes of the AF patients with heart failure enrolled in the CABANA trial (Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation).

METHODS: The CABANA trial randomized 2204 patients with AF who were ≥65 years old or <65 years old with ≥1 risk factor for stroke at 126 sites to ablation with pulmonary vein isolation or drug therapy including rate or rhythm control drugs. Of these, 778 (35%) had New York Heart Association class >II at baseline and form the subject of this article. The CABANA trial's primary end point was a composite of death, disabling stroke, serious bleeding, or cardiac arrest.

RESULTS: Of the 778 patients with heart failure enrolled in CABANA, 378 were assigned to ablation and 400 to drug therapy. Ejection fraction at baseline was available for 571 patients (73.0%), and 9.3% of these had an ejection fraction <40%, whereas 11.7% had ejection fractions between 40% and 50%. In the intention-to-treat analysis, the ablation arm had a 36% relative reduction in the primary composite end point (hazard ratio, 0.64 [95% CI, 0.41–0.99]) and a 43% relative reduction in all-cause mortality (hazard ratio, 0.57 [95% CI, 0.33–0.96]) compared with drug therapy alone over a median follow-up of 48.5 months. AF recurrence was decreased with ablation (hazard ratio, 0.56 [95% CI, 0.42–0.74]). The adjusted mean difference for the AFEQT (Atrial Fibrillation Effect on Quality of Life) summary score averaged over the entire 60-month follow-up was 5.0 points, favoring the ablation arm (95% CI, 2.5–7.4 points), and the MAFSI (Mayo Atrial Fibrillation-Specific Symptom Inventory) frequency score difference was –2.0 points, favoring ablation (95% CI, –2.9 to –1.2).

CONCLUSIONS: In patients with AF enrolled in the CABANA trial who had clinically diagnosed stable heart failure at trial entry, catheter ablation produced clinically important improvements in survival, freedom from AF recurrence, and quality of life relative to drug therapy. These results, obtained in a cohort most of whom had preserved left ventricular function, require independent trial verification.

REGISTRATION: URL: https://www.clinicaltrials.gov/ct2/show/NCT00911508; Unique identifier: NCT0091150.

Key Words: antiarrhythmic drug ■ atrial fibrillation ■ catheter ablation ■ heart failure ■ paroxysmal atrial fibrillation ■ persistent atrial fibrillation ■ pulmonary vein

Sources of Funding, see page 1388

https://www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- This study provides new randomized trial information regarding the benefits of catheter ablation in atrial fibrillation (AF) patients who have the clinical phenotype of heart failure.
- Specifically, we found that in the (CABANA) Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation trial there were substantial clinical outcome benefits with ablation over drug therapy in patients with New York Heart class II or III at trial entry, most of whom did not have a reduced ejection fraction.
- Benefits were evident for both all-cause mortality and AF reduction.
- However, the effects on heart failure hospitalizations were small and not significant.

What Are the Clinical Implications?

- This study suggests that catheter ablation may provide important prognostic and symptomatic benefits relative to drug therapy in patients with symptomatic AF, where symptoms and functional impairments are attributed to the combined effects of AF and heart failure.
- These results should not be viewed as practice changing until they are reproduced in a confirmatory trial of ablation in the same population.

Atrial fibrillation (AF) and heart failure (HF) often occur in the same patients and have a complex, incompletely understood interrelationship. In particular, although they have common antecedents, each also appears to promote development and progression of the other.[1] AF may lead to a decrease in ejection fraction (EF) and onset of symptomatic HF, particularly if the AF is sustained for long periods or produces high ventricular heart rates. Progressive heart muscle disease is also associated with a higher propensity to develop AF and to progress to more persistent forms of the disease. Optimal treatment of HF in patients with AF has been associated with improved maintenance of sinus rhythm.[2]

Several randomized clinical trials have reported that both AF and HF outcomes can be improved with catheter ablation.[3–11] Observational data have further suggested that ablation of AF is similarly effective in patients who have HF regardless of whether EF is preserved or reduced.[12,13] However, generalization from this evidence base to clinical practice is limited by important remaining uncertainties related to the modest number of randomized patients, the absence of any randomized trials in HF patients with preserved EF, and the substantial variations in methods and study cohort selection criteria used.

The CABANA trial (Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation), the largest trial to date of catheter ablation versus drug therapy in AF, found that the strategy of catheter ablation did not significantly improve the composite primary clinical outcome (death, disabling stroke, serious bleeding, or cardiac arrest) compared with drug therapy when analyzed by intention to treat (ITT).[14] Secondary end points of death or cardiovascular hospitalization and AF recurrence were significantly reduced by ablation, and quality of life (QoL) was improved out to 60 months.[14–16] In the prespecified subgroup analyses of patients with New York Heart Association (NYHA) Class II or greater HF symptoms recorded at baseline, ablation reduced the primary composite end point by 32%.[14] This article aimd to provide a more complete description of this subgroup, including a more comprehensive report of outcomes by treatment group.

METHODS

Trial Design and Setting

The CABANA trial design and methods have been reported previously in detail.[14,17] The institutional review board or ethics committee of each site approved the CABANA study, and written informed consent was obtained from all patients. Because this trial was funded by the US National Institutes of Health, the data used in our analysis, the material used to conduct the research, and the outcomes will be in the public domain within 2 years of the initial publication.

Study Population

Patients ≥18 years old with electrocardiographic documentation of at least 2 episodes of paroxysmal AF or 1 episode of persistent AF in the 6 months before enrollment and who were suitable candidates for either catheter ablation or drug therapies were eligible for enrollment.[17] To ensure sufficient event rates to detect a treatment effect, CABANA required patients to be either age ≥65 or age <65 years and to have at least 1 risk factor for stroke.[17] For the purpose of the present substudy, patients were included if they were identified by the enrolling site on the baseline case report form as having symptomatic NYHA class II HF or greater.

Outcomes

The primary end point in CABANA was a composite of all-cause mortality, disabling stroke, serious bleeding, or cardiac arrest.[17] Secondary end points included all-cause mortality alone, as well as the composite of all-cause mortality or cardiovascular hospitalization. HF-related mortality was adjudicated by the clinical events committee, and HF-related hospitalizations were designated by the site.

To capture AF recurrence, CABANA used a proprietary monitoring system to assess follow-up rhythm,[16] but not all countries were able to use that system because of regulatory issues. Of the 778 patients in this substudy, 330 (42%) used the CABANA system, and the remainder used available local

recording devices. The primary analysis of AF recurrence was prespecified to use the subset of patients with the CABANA monitoring system data. The 2 main AF recurrence measures were cumulative incidence of AF, estimated from end of blanking period, and AF burden, assessed as the percentage of time spent in AF during the 6-month interval, 96-hour Holter monitor recordings.

Two QoL instruments were used as coprimary end points in CABANA: the AFEQT (Atrial Fibrillation Effect on Quality of Life) and the MAFSI (Mayo Atrial Fibrillation–Specific Symptom Inventory), as reported previously.[15] The AFEQT is a 21-item instrument designed to assess AF-specific QoL in 3 domains: symptoms, daily activities, and treatment concerns. A summary score is calculated using 18 of the 21 items and ranges from 100 (no AF-related disability) to 0 (complete AF-related disability).[18] The first AFEQT item, "Are you currently in AF?" is not included in the summary score and is reported separately. On an individual patient level, an AFEQT score change of ≥5 is consistent with a clinically significant change.

The MAFSI is a modification of the Bubien–Kay Symptom Checklist[19] and in the version used for CABANA includes a 10-item symptom checklist that assesses both frequency and severity of each symptom over the past month.[19,20] Responses for the MAFSI frequency portion were collected with a 6-item Likert scale ranging from 0 (never) to 5 (always) and summed to generate a summary frequency score that has a theoretical range from 0 (no AF symptoms) to 40 (all 10 symptoms constant). The MAFSI severity score was collected with a 3-item Likert scale from 1 (mild) to 3 (severe) and summed to generate a summary score with a theoretical range from 0 (no AF symptoms) to 30 (all 10 symptoms at the most severe level). Patient-level benchmarks for interpretation of changes in MAFSI scales are ≈1.6 or more points for the frequency scale and 1.3 points for the severity scale.[15] QoL data were collected by structured interview at baseline, 3 and 12 months, and annually thereafter, as described previously.[15]

Verification of HF Classification Using Baseline QoL Data

HF remains an inexact phenotypic clinical diagnosis based primarily on expert clinician integration of multiple different types of data.[21] CABANA did not collect specific biomarker or other clinical or test data relevant to the diagnosis of HF. Left ventricular function imaging was assumed to be part of routine care and was collected as available.

We examined select baseline patient-reported functional status and symptom data relevant to the NYHA functional classification and to the clinical diagnosis of HF. From the Duke Activity Status Index, we calculated the proportion of subjects who could do each of 5 activities of progressive workload "with no difficulty." Using the 36-Item Short Form Survey physical function scale, we similarly calculated the proportion of subjects who could do 8 activities representing a progressive physical workload "with no limitations." Last, using the MAFSI frequency questions, we calculated the proportion of subjects with 5 different frequency levels (never to always) of "shortness of breath" and "tired/lack of energy." For these descriptive comparisons, patients were classified as no HF/NYHA class I, NYHA class II, and NYHA class III.

Statistical Analysis

Descriptive summary statistics included counts (percentages) for categorical variables and medians (25th and 75th percentiles) for continuous variables. The primary statistical comparisons were performed with treatment assigned as randomized (ITT).[14] Kaplan–Meier cumulative event rates were estimated for each treatment group with time-to-event measured (in months) from the time of randomization.[22] Treatment effect sizes for most clinical outcomes were expressed as hazard ratios (HRs) with associated 95% CIs and were estimated using a covariate adjusted Cox proportional hazards model.[23] The Cox model was constructed as a stratified model (NYHA class II or greater versus all others) using the entire CABANA cohort and was adjusted for the following list of prespecified baseline patient characteristics: age, sex, race or ethnicity, AF type, years since onset of AF, history of HF, structural heart disease, CHA_2DS_2-VASc score, history of coronary artery disease, and hypertension. An interaction term, *treatment group* × *HF* (defined by NYHA class II or greater) was included in the model. Statistical testing of treatment differences was performed with the Wald test from the Cox model.

Recurrent AF incidence rates were estimated using a Fine–Gray model[24] adjusted for baseline covariates listed earlier, with death treated as a competing risk.

The QoL end points were analyzed with a repeated-measure, mixed-effects model with baseline score and month 3, 12, 24, 36, 48, and 60 responses included as outcomes and time, treatment group, and time × treatment group included as fixed effects.[15] For each follow-up point, we generated point estimates for each treatment group, as well as treatment group mean differences (ablation score – drug score). Precision of estimates was assessed with 95% CIs. Because the model does not require either complete data on all patients or a uniform length of follow-up, we did not impute missing values.

P values, where provided, are intended as adjunctive interpretive aids reflecting the level of unexpected observed effects under the null hypothesis.[25] No adjustments were made for multiple comparisons. The HF subgroup comparison was a prespecified secondary analysis in CABANA. However, when that specification was made in the study protocol in 2009, we had no strong a priori reason to suspect that treatment benefits would be substantially larger in HF patients than in other patients enrolled in CABANA.

Prespecified and Post Hoc Sensitivity Analyses

Given the complexities involved in interpreting an ITT analysis of a procedure-based comparison where crossover is possible, we prespecified 2 sensitivity analyses for the method of treatment assignment.[14] *As treated* comparisons were performed using a Cox model with catheter ablation included as a time-dependent covariate. *Per protocol* comparisons were performed in which the drug treatment arm consisted of patients randomized to drug therapy without crossover to ablation. Drug arm patients who crossed over to catheter ablation were censored at the time of the ablation. The ablation treatment arm consisted of patients randomized to ablation who received the procedure within a 6-month window after randomization. Comparisons were adjusted for baseline covariates listed earlier.

Because baseline EF was missing in 27% of patients, the statistical method of multiple imputation[26] was used to impute the missing values, under the assumption of missingness at randomization. Multiple imputation was carried out by creating 25 imputed datasets using PROC MI in SAS version 9.4 (SAS Institute, Inc, Cary, NC) with the method of fully conditional specification. A sensitivity analysis was conducted with a covariate-adjusted model including an interaction term between treatment group and the baseline EF, with and without the imputed values.

RESULTS

Baseline Characteristics

Of the 2204 patients randomized in CABANA, 778 had NYHA class II or greater at baseline (Figure I in the Data Supplement). Patient characteristics were well balanced between the groups, and overall had a median age of 68 years; 44% were female and 76% were NYHA class II (Table 1). Paroxysmal AF was present in 31.6%, persistent AF in 55.3%, and longstanding persistent in 13.1%. At enrollment, 75% of patients were taking a β-blocker, and 64% were on an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker. A baseline EF was available for 571 patients (73%; Table 1; Figure I in the Data Supplement). Of these, 79% had an EF ≥50%, 11.7% had an EF between 40% and 49%, and 9.3% had an EF <40%. Comparisons of the baseline characteristics of patients with and without HF in CABANA are provided in Table I in the Data Supplement. As shown in Table II in the Data Supplement, baseline patient-reported functional status and symptoms of dyspnea and fatigue showed a clear gradient associated with clinician-reported baseline NYHA class such that worse NYHA class was associated with greater reductions in physical functioning and more frequent dyspnea and fatigue.

Treatment Data

In the ablation group, 344 HF patients (91.0%) underwent ablation at a median of 24 days after randomization, whereas 34 patients (9.0%) did not receive ablation. Among the catheter ablation patients with HF and postblanking follow-up, 155 (47%) of 330 were on a rhythm control drug at the end of the blanking period (Table III in the Data Supplement), and 76 (23%) of 325 were on a rhythm control drug at the latest of 1 or more follow-up contacts.

In the drug therapy alone group, 89 (22.3%) received an ablation procedure at a median of 351 days after randomization (25th percentile, 162; 75th percentile, 725). At the end of the blanking period, 307 (80%) of 383 were on a rhythm control drug (Table III in the Data Supplement), and 188 (50%) of 376 were receiving 1 of these drugs at the latest of 1 or more follow-up contacts.

The most common treatment-related adverse events in the ablation arm included hematoma (3.2%), pseudoaneurysm (1.2%), esophageal ulcer (1.2%), and severe pericardial chest pain (0.6%). The most common treatment-related adverse events in the drug therapy arm included hyper- or hypothyroidism (2.5%), gastrointestinal abnormality excluding moderate or severe diarrhea (1.3%), major proarrhythmic event (0.8%), and liver injury or failure (0.5%).

Clinical Outcome Comparisons by ITT

The CABANA primary outcome event (death, disabling stroke, serious bleeding, or cardiac arrest) occurred in 34 (9.0%) of 378 HF patients in the catheter ablation group and in 49 (12.3%) of 400 HF patients in drug therapy (HR for ablation versus drug therapy, 0.64 [95% CI, 0.41–0.99]; Figure 1). Death from any cause occurred in 23 (6.1%) of 378 HF patients in the ablation arm and 37 (9.3%) of 400 HF patients in the drug therapy arm (HR, 0.57 [95% CI, 0.33–0.96]; Figure 2). Death from cardiovascular causes occurred in 12 (3.2%) of 378 patients in the ablation arm and 14 (3.5%) of 400 patients in the drug therapy arm (HR, 0.70 [95% CI, 0.31–1.57]). Deaths attributed to HF occurred in 6 patients in the ablation arm and 4 patients in the drug therapy arm. Death or cardiovascular hospitalization occurred in 212 (56.1%) of 378 patients in the ablation arm and 245 (61.3%) of 400 patients in the drug therapy arm (HR, 0.84 [95% CI, 0.70–1.02]). HF hospitalization occurred in 34 (9.0%) of 378 patients in the ablation arm and 37 (9.3%) of 400 patients in the drug therapy arm (HR, 0.89 [95% CI, 0.56–1.44]).

Treatment Assignment Sensitivity Analyses

In a prespecified as-treated analysis, the ablation arm showed a 42% reduction in the primary composite end point (HR, 0.58 [95% CI, 0.37–0.90]) in HF patients. Reductions were also seen in all-cause mortality (HR, 0.50 [95% CI, 0.30–0.85]), the composite of death or cardiovascular hospitalization (HR, 0.84 [95% CI, 0.70–1.01]), and the composite of death or HF hospitalization (HR, 0.59 [95% CI, 0.41–0.87]). No deaths occurred within the first 30 days after initiation of either therapy. One disabling stroke occurred within the first 30 days of treatment after initiation of drug therapy.

In a per-protocol analysis, patients in the ablation arm who received catheter ablation within 6 months showed reduction in the primary composite end point (HR, 0.60 [95% CI, 0.38–0.94]) and all-cause mortality (HR, 0.52 [95% CI, 0.31–0.90]).

Table 1. Baseline Demographics and Clinical Characteristics in CABANA Heart Failure Patients

Variable	Ablation group (N=378), n/N (%)*	Drug group (N=400), n/N (%)*	All patients (N=778), n/N (%)*
Baseline characteristics			
Age			
Median (Q1, Q3)	68 (62, 73)	67 (62, 73)	68 (62, 73)
<65 y	130/378 (34.4%)	154/400 (38.5%)	284/778 (36.5%)
65 to <75 y	184/378 (48.7%)	179/400 (44.8%)	363/778 (46.7%)
≥75 y	64/378 (16.9%)	67/400 (16.8%)	131/778 (16.8%)
Female sex	171/378 (45.2%)	174/400 (43.5%)	345/778 (44.3%)
Minority: Hispanic or non-White†	29/378 (7.7%)	32/400 (8.0%)	61/778 (7.8%)
Body mass index, median (Q1, Q3), kg/m^2	31 (27, 35)	31 (27, 36)	31 (27, 35)
Canadian Cardiovascular Society severity of atrial fibrillation‡			
Class 0	29/378 (7.7%)	22/399 (5.5%)	51/777 (6.6%)
Class 1	37/378 (9.8%)	43/399 (10.8%)	80/777 (10.3%)
Class 2	135/378 (35.7%)	143/399 (35.8%)	278/777 (35.8%)
Class 3	144/378 (38.1%)	159/399 (39.8%)	303/777 (39.0%)
Class 4	33/378 (8.7%)	32/399 (8.0%)	65/777 (8.4%)
New York Heart Association classification§			
Class II	277/378 (73.3%)	315/400 (78.8%)	592/778 (76.1%)
Class III	99/378 (26.2%)	85/400 (21.3%)	184/778 (23.7%)
Class IV	2/378 (0.5%)	0/400 (0.0%)	2/778 (0.3%)
Medical history			
Hypertension (>140/90 mm Hg)	316/378 (83.6%)	349/400 (87.3%)	665/778 (85.5%)
Diabetes (glucose ≥126 mg/dL)	97/378 (25.7%)	98/400 (24.5%)	195/778 (25.1%)
Previous cerebral vascular accident or transient ischemic attack	39/378 (10.3%)	40/400 (10.0%)	79/778 (10.2%)
Coronary artery disease	80/378 (21.2%)	90/400 (22.5%)	170/778 (21.9%)
History of congestive heart failure	111/378 (29.4%)	118/399 (29.6%)	229/777 (29.5%)
Sleep apnea	72/378 (19.0%)	82/400 (20.5%)	154/778 (19.8%)
Chronic kidney disease (eGFR <60 mL/min/1.73 m^2)	91/369 (24.7%)	90/386 (23.3%)	181/755 (24.0%)
Left ventricular ejection fraction, median (Q1, Q3)	55 (50, 60)	56 (50, 62)	55 (50, 61)
Left ventricular ejection fraction ≤35%	22/285 (7.7%)	23/286 (8.0%)	45/571 (7.9%)
CHA_2DS_2-VASc score‖			
Median (Q1, Q3)	3 (2, 4)	3 (2, 4)	3 (2, 4)
0–1	50/378 (13.2%)	55/400 (13.8%)	105/778 (13.5%)
2	83/378 (22.0%)	90/400 (22.5%)	173/778 (22.2%)
3	110/378 (29.1%)	112/400 (28.0%)	222/778 (28.5%)
4	73/378 (19.3%)	71/400 (17.8%)	144/778 (18.5%)
≥5	62/378 (16.4%)	72/400 (18.0%)	134/778 (17.2%)
Arrhythmia history			
Years since onset of atrial fibrillation: median (Q1, Q3)	1.1 (0.2, 3.7)	1.2 (0.3, 4.2)	1.1 (0.3, 4.1)
Type of atrial fibrillation at enrollment			
Paroxysmal	110/378 (29.1%)	136/400 (34.0%)	246/778 (31.6%)
Persistent	221/378 (58.5%)	209/400 (52.3%)	430/778 (55.3%)
Longstanding persistent	47/378 (12.4%)	55/400 (13.8%)	102/778 (13.1%)
Previous hospitalization for atrial fibrillation	170/378 (45.0%)	186/400 (46.5%)	356/778 (45.8%)
Previous direct current cardioversion for atrial fibrillation	135/378 (35.7%)	160/400 (40.0%)	295/778 (37.9%)

(*Continued*)

Table 1. Continued

Variable	Ablation group (N=378), n/N (%)*	Drug group (N=400), n/N (%)*	All patients (N=778) n/N (%)*
History of atrial flutter	38/371 (10.2%)	49/393 (12.5%)	87/764 (11.4%)
Previous ablation for atrial flutter	11/377 (2.9%)	22/398 (5.5%)	33/775 (4.3%)
No. of rhythm control drugs¶			
0	200/354 (56.5%)	191/379 (50.4%)	391/733 (53.3%)
1	127/354 (35.9%)	150/379 (39.6%)	277/733 (37.8%)
≥2	27/354 (7.6%)	38/379 (10.0%)	65/733 (8.9%)

No baseline demographics or clinical characteristics demonstrated a statistically significant difference between the treatment groups presented in this table. CABANA indicates Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation; and eGFR, estimated glomerular filtration rate calculated using Chronic Kidney Disease Epidemiology Collaboration creatinine equation; Q1 and Q3, quartiles (25th and 75th percentiles).

*Unless otherwise noted.

†Race/minority was determined by the site investigator in conjunction with the patient on the basis of predefined categories as required by the National Institutes of Health's specified categories.

‡On a scale of 0 to 4 in which 0 is the least severe and 4 is the most severe symptom of atrial fibrillation.

§On a scale of I to IV in which I is the least severe and IV is the most severe symptom of heart failure.

‖On a scale of 0 to 9 in which 0 is the lowest risk of stroke and 9 is the highest risk of stroke.

¶Current or past use of rhythm control therapy reported at the time of enrollment.

Subgroup Analyses

Analyses of prespecified subgroups in the HF cohort by ITT using the primary composite end point were consistent with the overall CABANA trial (Figure 3).

After using multiple imputation to impute missing baseline EF values, 9.8% had an EF <40%, 15.6% had an EF 40% to 49%, and 74.6% had an EF ≥50%. In a post hoc analysis, ablation reduced mortality by 60% relative to drug therapy in the patients with EF ≥50% (HR, 0.40 [95% CI, 0.18–0.88]) with 4-year Kaplan–Meier mortality rates of 3.3% versus 8.6% (Table IVa and IVb and Figure II in the Data Supplement). Analysis with complete EF data showed HR of 0.51 (95% CI, 0.23–1.12) and 4-year Kaplan–Meier mortality rates (4.2% versus 8.3%). In EF 40% to 49%, which included patients with imputed EFs, the HR for the ablation effect on mortality was 0.43 (95% CI, 0.09–2.13). Not enough patients were in this subgroup excluding the imputed EF patients or in the subgroup with EF <40% (with or without imputation) to reliably estimate a treatment effect on mortality (Table IV in the Data Supplement).

AF Recurrence

Of the 778 HF patients, 330 (42.4%) used the CABANA recording system to detect AF recurrence after the blanking period. By 12 months, 37% of the HF ablation arm patients and 58% of the HF drug therapy arm patients recorded a recurrence of any AF (Figure 4). At 5 years, the corresponding values were 56% (ablation

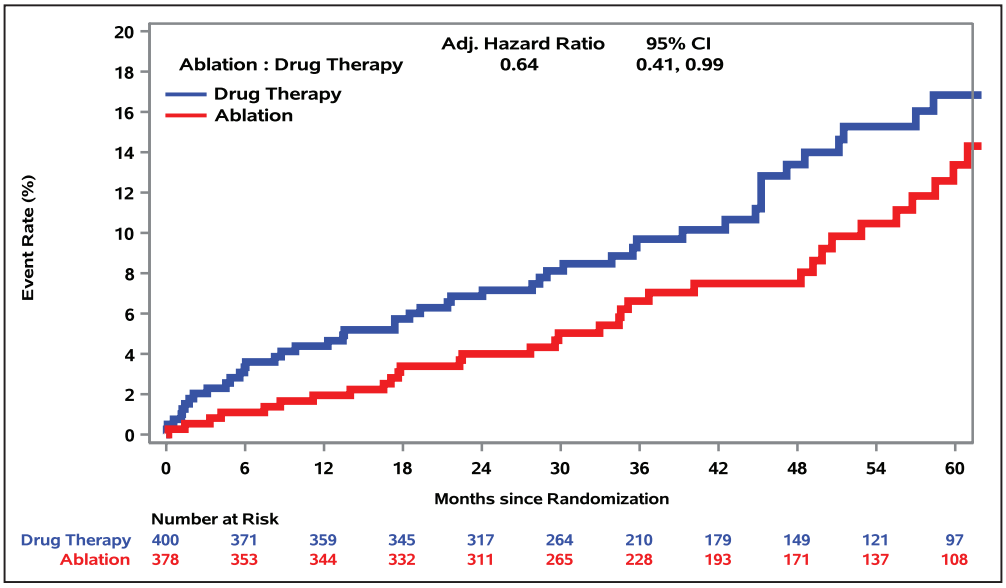

Figure 1. Primary composite end point (death, disabling stroke, serious bleeding, or cardiac arrest) Kaplan-Meier curves by intention-to-treat among CABANA heart failure patients.

CABANA indicates Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation.

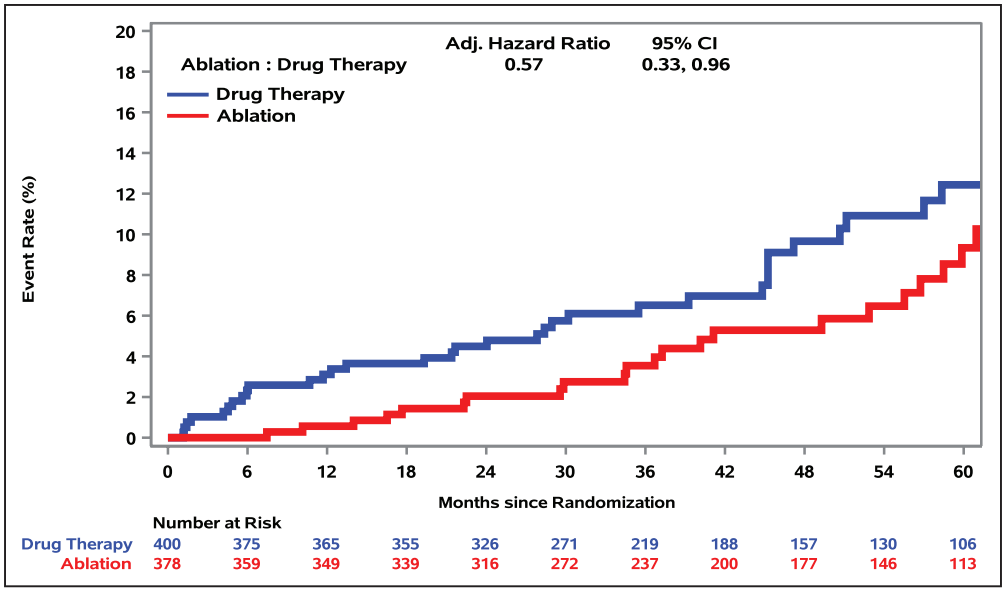

Figure 2. All-cause mortality Kaplan-Meier curves by intention-to-treat among CABANA heart failure patients.
CABANA indicates Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation.

arm) and 72% (drug arm). Overall, the ablation arm had a 44% relative reduction in first AF recurrence when compared with the drug arm (HR, 0.56 [95% CI, 0.42–0.74]). AF burden at baseline showed an average of 57.8% of the CABANA Holter recording time was spent in AF. At 12 months, AF burden averaged 7% in the ablation arm and 18% in the drug therapy arm. At 5 years, the corresponding percentages were 17% and 26%, respectively. At all follow-up time points, the AF burden was lower in the ablation arm relative to the

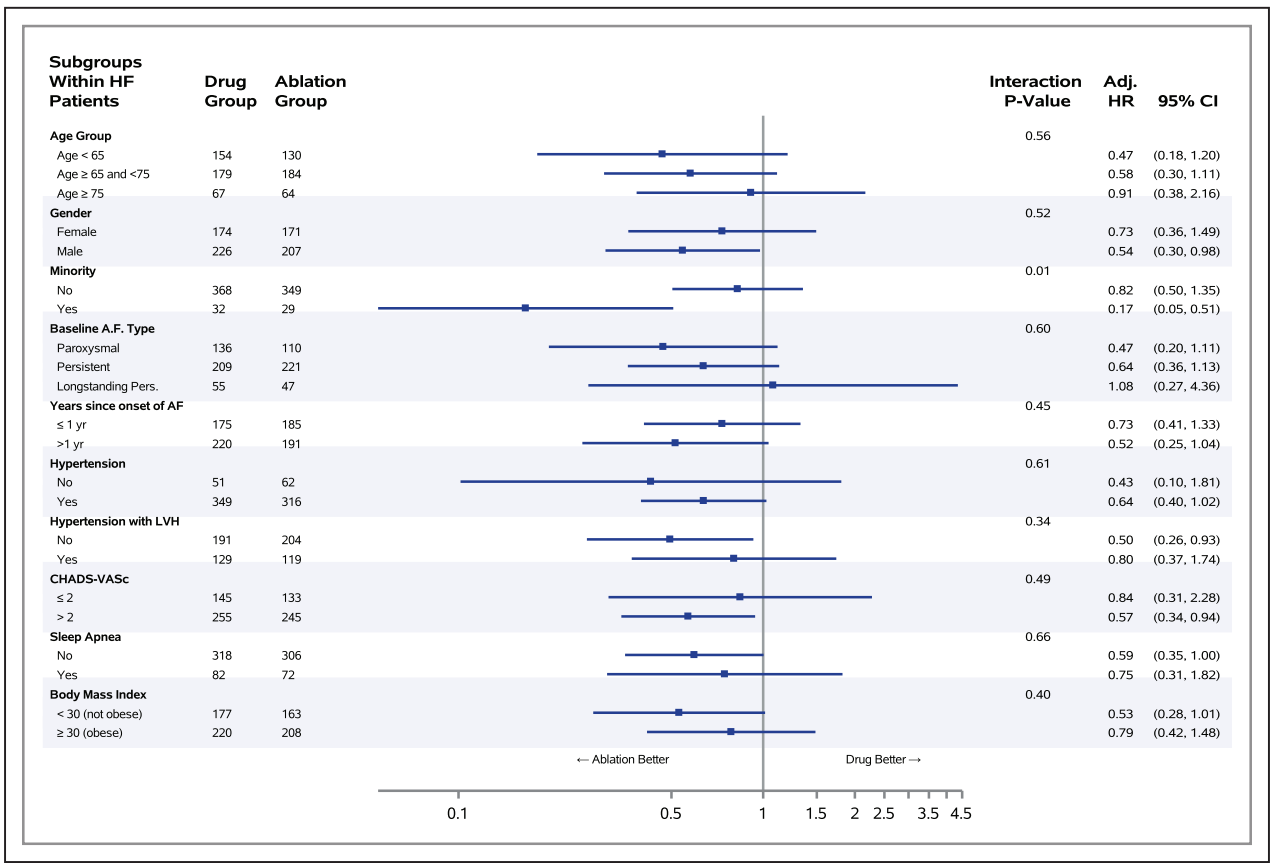

Figure 3. Forest plot of prespecified subgroup comparisons in CABANA heart failure patients.
AF indicates atrial fibrillation; CABANA, Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation; HF, heart failure; and HR, hazard ratio.

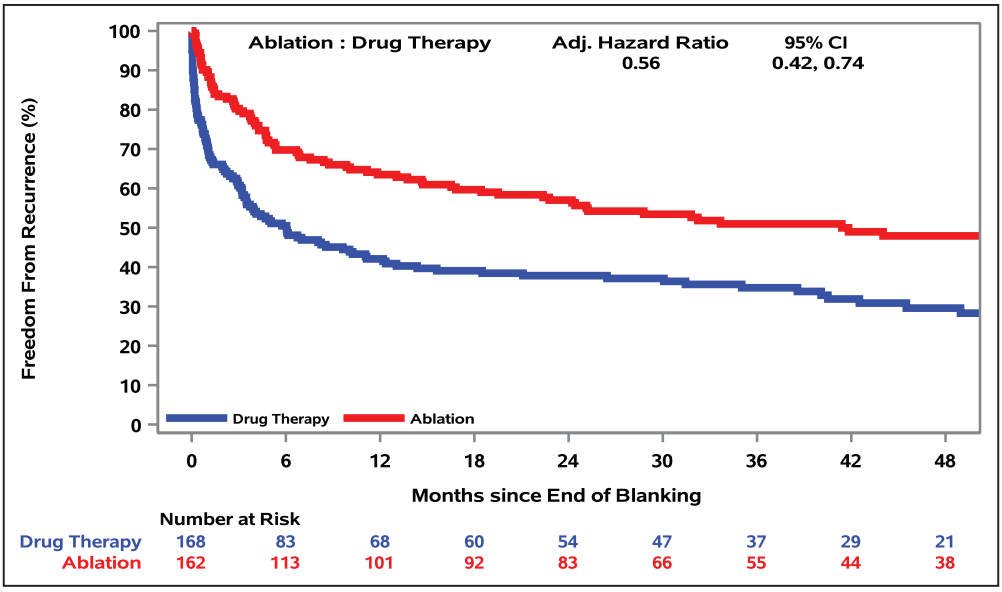

Figure 4. Cumulative incidence curves of first recurrence of atrial fibrillation in the postblanking period among CABANA heart failure patients who used the CABANA ECG recording system.
CABANA indicates Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation.

drug therapy arm (Figure 5). Ablation also had lower burden regardless of AF type recorded at baseline (Figure III in the Data Supplement).

AF-Related QoL Outcomes

Mean AFEQT summary scores were equivalent at baseline in the 2 treatment arms (median 57 ablation arm, 56 drug therapy arm) and higher (more favorable) at each follow-up assessment out to 60 months in the ablation arm (Table 2). The adjusted mean difference at 12 months was 5.7 points, favoring the ablation arm (95% CI, 2.8–8.7 points). The adjusted mean difference averaged over the entire 60-month follow-up was 5.0 points, favoring the ablation arm (95% CI, 2.5–7.4 points; Table 2; Figure IV in the Data Supplement).

Mean MAFSI frequency scores were equivalent at baseline (median 13 in each arm; Table 2). At 12 months, MAFSI scores were more favorable (lower) in the ablation arm (Figure 6A; adjusted mean treatment group difference, –1.9 [95% CI, –3.0 to –0.9]). Over the 60 months of follow-up, the average adjusted MAFSI score difference was –2.0 points, favoring ablation (95% CI, –2.9 to –1.2; Figure 6B; Table 2). A similar pattern was seen for the MAFSI severity score (Table 2).

DISCUSSION

Catheter ablation in CABANA trial patients with AF and class II or greater HF produced clinically consequential reductions in all-cause mortality (43% relative reduction, 3.1 per 100 absolute reduction at 5 years), as well as a lower AF recurrence rates (44% reduction in time to first recurrence) and AF burden. Ablation patients also demonstrated substantial and sustained improvements in QoL out to 5 years. Although these treatment benefits appear plausible, they clearly need to be confirmed with an adequately sized clinical trial of ablation in HF subjects.[27–31]

CABANA is the first large randomized trial to describe an important mortality benefit from AF treatment in HF subjects who predominately have preserved systolic function. One of the main objectives of the CABANA trial was to test whether effectively treating the AF state could reduce the excess mortality risk associated with AF.[17] CABANA was originally powered to detect a 30% relative mortality reduction. Although the effect of ablation on all-cause mortality relative to drug therapy was indeterminate in the overall 2204 patient CABANA cohort (HR, 0.85 [95% CI, 0.60–1.21]), initial subgroup analyses (of the trial primary composite outcome measure) suggested that the treatment effect in the subset of 778 patients with HF (NYHA class II or III) was substantially larger.[14] The present article, part of the prespecified CABANA research program, provides substantial new information on the HF subgroup treatment effects.

AF and Risk of Mortality

The morbidity of AF has been recognized for many decades, but the recognition that the development of and presence of AF is also associated with a higher mortality risk is more recent.[32–35] Some of this excess mortality risk has been attributed to associated heart diseases leading to the AF, such as valvular or coronary disease, but AF appears to have important adverse effects on survival even in the absence of such associations and for reasons other than inadequate anticoagulation leading to major stroke.[36,37]

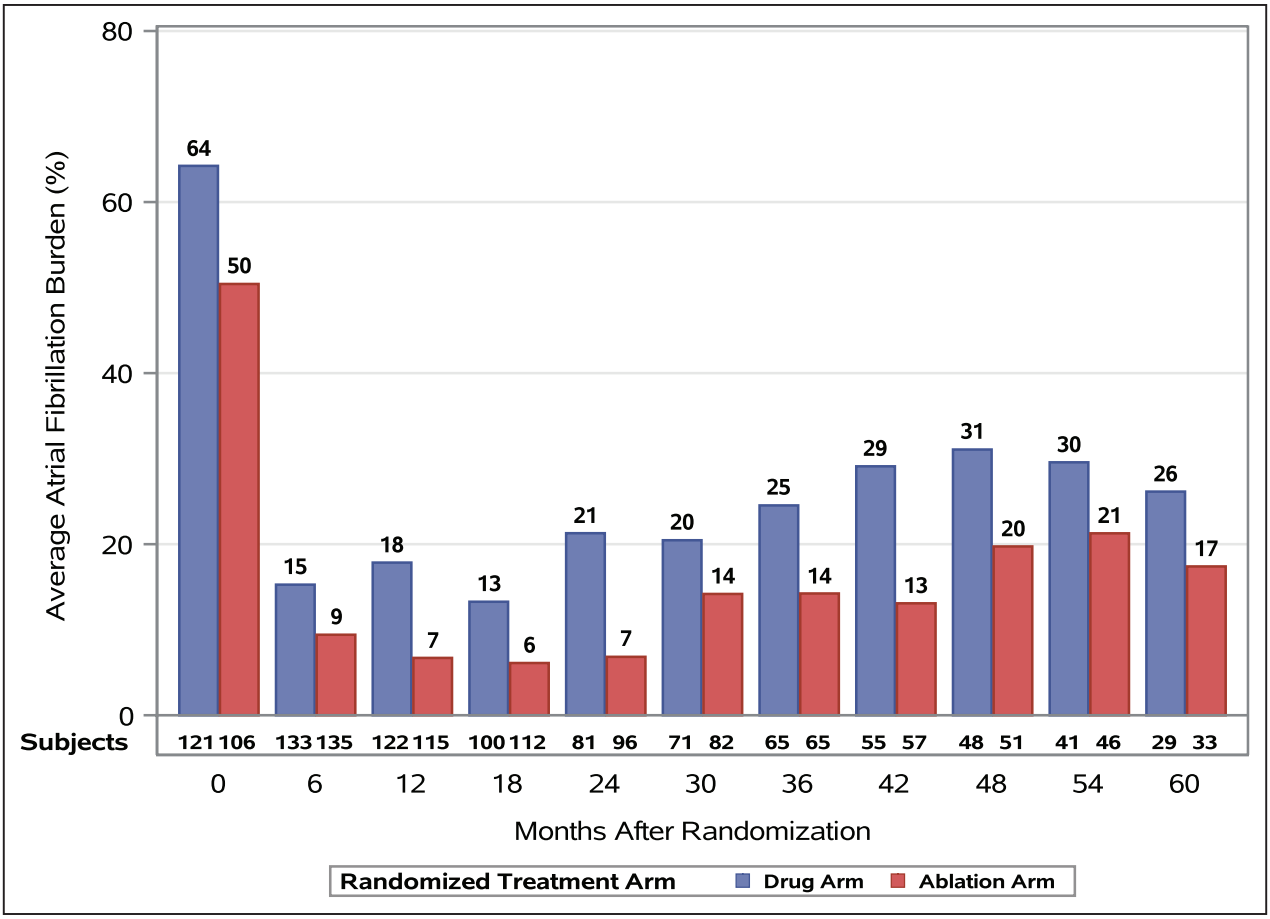

Figure 5. Atrial fibrillation burden by time and randomization assignment among CABANA heart failure patients who used the CABANA ECG recording system.
CABANA indicates Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation.

The Women's Health Study, involving almost 35,000 subjects initially free of cardiovascular disease who were followed for a median of 15 years found that new AF was associated with a 2-fold increase in adjusted risk for all-cause death and a 4-fold increase in adjusted risk for cardiovascular death.[38] Accounting for nonfatal events (myocardial infarction, stroke, HF) modestly reduced the size of these risks but did not eliminate the associations. The question of whether AF causes some or all of this excess mortality or is simply a marker for factors that are the true causes remains unsettled. Clinical trial evidence supporting the ability of ablation to reduce mortality relative to drug therapy is needed to resolve the issue. CABANA adds important new evidence in this area, pointing particularly to the need for a larger confirmatory trial specifically in the HF population.

Previous Clinical Trial Evidence of Effects of Ablation in HF

A number of relatively small randomized trials have been published comparing catheter ablation with drug therapy in AF patients with HF.[3–11] Most were limited to subjects with systolic dysfunction, with predominately NYHA class II or III symptoms and persistent AF. Only 3, CASTLE-HF (Catheter Ablation for Atrial Fibrillation with Heart Failure), AATAC (Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device), and AMICA (Catheter Ablation Versus Best Medical Therapy in Patients With Persistent Atrial Fibrillation and Congestive Heart Failure),[4,7,9] randomized >100 patients. Summary effect sizes included an ≈50% reduction in all-cause mortality, a 40% reduction in HF hospitalizations, and a 9-point improvement in Minnesota Living with HF scores. The effects on brain natriuretic peptide, 6-minute walk, and oxygen consumption have been variable.[4–6,8–10] AF recurrence was decreased by 34% with ablation. These trials also suggested that ablation improved EF by an absolute 7%, although no difference with drug therapy was seen in the AMICA trial.[7] No evidence was found for an increase in serious adverse effects with ablation.

Effects of Ablation in HF With Preserved EF

No randomized controlled trials have tested ablation versus drug therapy in HF patients with preserved

Table 2. Quality-of-Life Outcomes in CABANA Heart Failure Patients

Time point	Catheter ablation (N=378)			Drug therapy (N=400)			Adjusted difference (95% CI)
	Median (Q1, Q3)	Mean (SD)	N	Median (Q1, Q3)	Mean (SD)	N	
AFEQT summary score Scale: 0=complete disability, 100=no disability							
Baseline	57 (44, 73)	57.6 (19.9)	371	56 (44, 73)	57.7 (19.9)	394	–0.1 (–2.9 to 2.7)
3 mo	79 (63, 91)	75.7 (18.9)	329	72 (55, 90)	70.6 (21.5)	356	4.9 (1.9 to 7.9)*
12 mo	86 (68, 97)	80.6 (19.8)	310	80 (59, 93)	75.0 (19.6)	317	5.7 (2.8 to 8.7)*
24 mo	86 (70, 97)	80.9 (18.8)	285	78 (60, 92)	74.4 (21.1)	280	5.9 (2.8 to 9.0)*
36 mo	87 (70, 96)	81.8 (17.7)	204	82 (67, 94)	77.8 (20.1)	203	4.0 (0.6 to 7.3)
48 mo	85 (68, 97)	80.7 (18.5)	144	82 (61, 93)	76.1 (20.1)	146	4.6 (0.9 to 8.4)
60 mo	86 (69, 96)	80.5 (18.9)	106	81 (58, 94)	75.0 (22.3)	101	4.5 (-0.3 to 9.3)
All follow-up	85 (68, 96)	79.7 (19.0)	1378	78 (59, 93)	74.3 (20.8)	1403	5.0 (2.5 to 7.4)
MAFSI frequency score Scale: 0=never symptoms, 40=always symptoms							
Baseline	13 (9, 17)	13.3 (5.9)	371	13 (8, 18)	13.3 (6.4)	389	–0.0 (-0.9 to 0.9)
3 mo	8 (4,12)	8.5 (6.2)	300	10 (5, 15)	10.7 (6.9)	328	–2.1 (–3.1 to –1.1)*
12 mo	7 (2,12)	8.1 (6.7)	291	10 (5, 14)	9.9 (6.5)	295	–1.9 (–3.0 to –0.9)*
24 mo	7 (2, 12)	7.9 (6.5)	271	10 (5, 15)	10.5 (7.1)	245	–2.2 (–3.3 to –1.1)*
36 mo	8 (3, 13)	8.2 (6.3)	195	9 (4, 15)	10.0 (6.9)	189	–1.9 (–3.1 to –0.7)
48 mo	7 (2, 12)	7.8 (6.6)	138	9 (5, 13)	9.8 (7.0)	133	–1.7 (–3.1 to –0.3)
60 mo	6 (2, 12)	7.8 (6.7)	102	9 (6, 15)	10.2 (6.8)	93	–2.3 (–4.0 to –0.7)
All follow-up	7 (3, 12)	8.1 (6.4)	1297	10 (5, 15)	10.2 (6.8)	1283	–2.0 (–2.9 to –1.2)*
MAFSI severity score Scale: 0=mild symptoms, 30=extreme symptoms							
Baseline	10 (7, 13)	10.5 (4.7)	372	10 (7, 14)	10.5 (5.1)	385	–0.0 (–0.7 to 0.7)
3 mo	6 (3, 11)	6.8 (4.9)	297	8 (4, 13)	8.6 (5.6)	328	–1.7 (–2.5 to –0.9)*
12 mo	5 (2, 10)	6.5 (5.4)	291	8 (4, 12)	8.0 (5.2)	295	–1.5 (–2.3 to –0.7)*
24 mo	5 (2, 9)	6.3 (5.2)	270	7 (4, 12)	8.1 (5.5)	243	–1.5 (–2.3 to –0.6)*
36 mo	6 (2, 10)	6.6 (5.1)	193	8 (3, 12)	7.9 (5.7)	189	–1.5 (–2.5 to –0.5)
48 mo	6 (2, 10)	6.2 (5.1)	137	7 (3, 10)	7.3 (5.3)	133	–0.9 (–2.0 to 0.2)
60 mo	5 (2, 9)	6,5 (5.7)	102	7 (4, 11)	7.9 (5.3)	93	–1.3 (–2.7 to 0.1)
All follow-up	6 (2, 10)	6.5 (5.2)	1290	7 (4, 12)	8.1 (5.5)	1281	–1.4 (–2.1 to –0.7)*

AFEQT summary score interpretive guidance: <70=severely symptomatic, 70–89=mildly to moderately symptomatic, ≥90=minimally symptomatic or asymptomatic; clinically important change 5.0. MAFSI frequency score interpretive guidance: >9=severely symptomatic, 4–9=mildly to moderately symptomatic, <4=minimally symptomatic or asymptomatic; clinically important change 1.6. MAFSI severity score interpretive guidance; clinically important change 1.3. AFEQT indicates Atrial Fibrillation Effect on Quality of Life; and MAFSI, Mayo Atrial Fibrillation-Specific Symptom Inventory.

*P values <0.001.

EF. The available evidence consists of a few, mostly small, observational reports of ablation outcomes in this population.[13,39,40] A retrospective single-center cohort study of 230 HF patients (97 with reduced EF, 133 with preserved EF, 62% to 63% in both subgroups with nonparoxysmal AF) found effectiveness of ablation in producing freedom from recurrent AF, and improvement in QoL did not vary as a function of baseline ventricular function.[12] Analysis of a large US claims database of 289 366 patients with AF and HF (identified by *International Classification of Diseases* codes) reported that, of the 7465 who received ablation, 57% had preserved EF.[41] Comparison of ablation versus drug therapy in HF patients with versus without reduced EF showed no difference in treatment effect size. In CABANA, 79% of HF patients with EF measured at baseline had values ≥50%.

AF Recurrence in HF

Freedom from recurrent AF in the HF subgroup was very similar to that previously reported in the overall CABANA trial both when assessed as time to first recurrence (HR 0.56 for HF subgroup, 0.52 for overall trial) and as AF burden (at 12 months 7% in ablation patients in HF subgroup versus 6% in overall trial, 18% in drug arm of HF subgroup versus 14% in overall trial). Thus, in the context of the HF patients selected for CABANA with predominantly preserved LV function and the subset of those who had access to the CABANA ECG recording system, HF was not associated with inferior

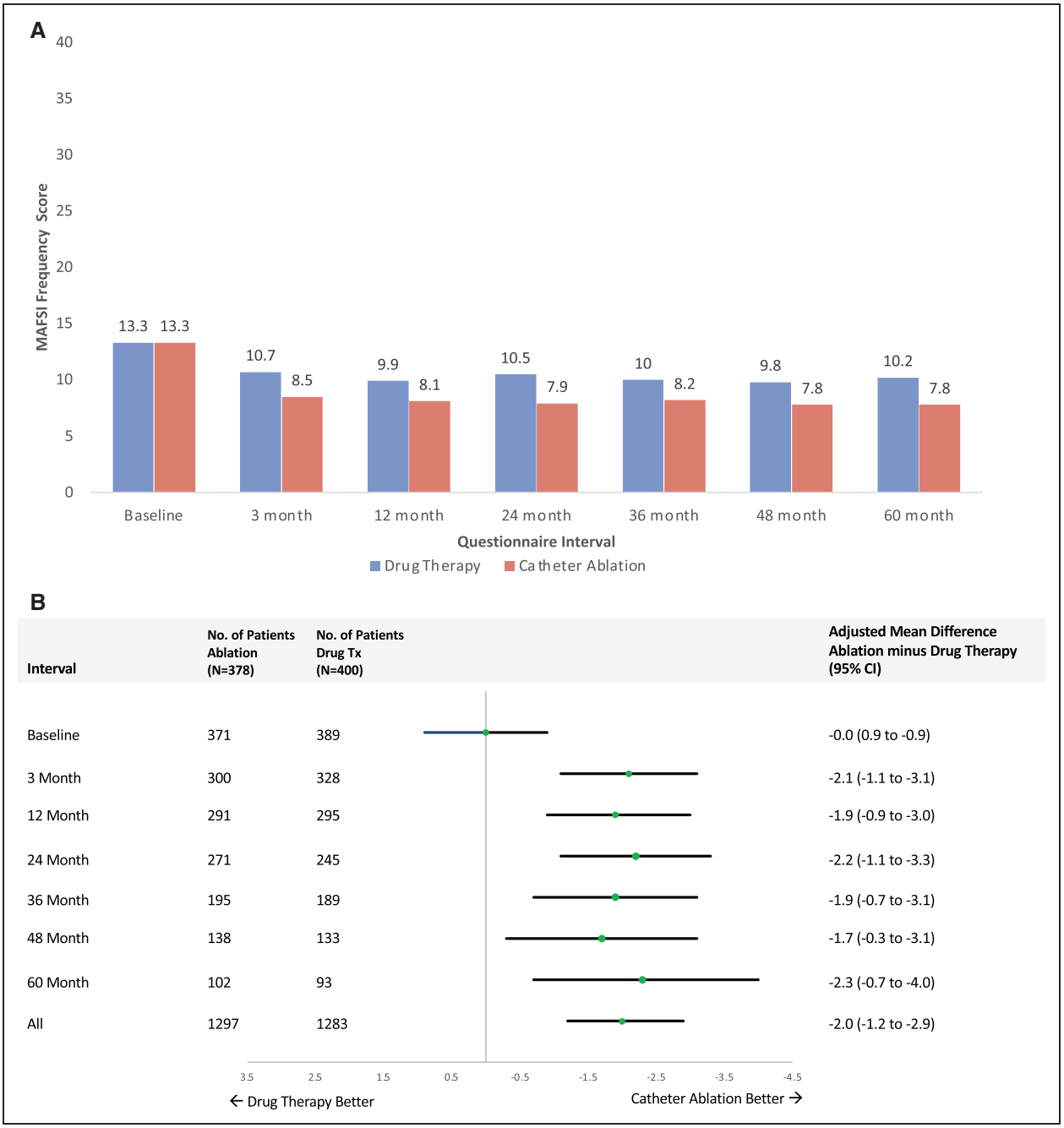

Figure 6. Quality-of-life outcomes in CABANA heart failure patients by MAFSI (Mayo Atrial Fibrillation-Specific Symptom Inventory) scoring.
CABANA indicates Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation.

technical results with ablation. Ablation had superior results at 12 months in patients with both paroxysmal and with persistent or longstanding persistent AF. More attenuation of treatment differences appears present in the latter subgroup (Figure III in the Data Supplement), but samples are small and precision relatively low.

QoL in HF

AFEQT summary scores, reflecting the impact of AF on symptoms, activities, and treatment concerns, showed greater impairments in HF patients relative to the overall trial cohort (baseline median scores, 56–57 points in HF patients versus 63 in overall CABANA cohort).[15] As reported previously, both treatment groups in CABANA demonstrated a substantial improvement over the first 12 months of study participation, after which QoL values at the cohort level showed little change. In addition to these changes, mean treatment group differences were larger in favor of ablation at all assessment points out to 60 months. Similar patterns were seen for the MAFSI

frequency and severity scores. These findings complement the clinical outcome data by providing a patient perspective on the treatment effects studied in CABANA. The results reported in the present article provide new evidence of a substantial, clinically important incremental benefit from ablation on QoL in a cohort of HF patients with predominantly preserved left ventricular function.

Adverse Effects of Treatment

Catheter ablation has the potential to harm subjects either by major procedural complications that occur in temporal proximity to the procedure or later because of adverse cardiac remodeling. Early complications can include perforation by catheters or excessive ablative energy-related injury to adjacent tissues. Such complications were infrequent in CABANA, with no procedure-related deaths recorded.[14] In addition, in the present substudy we found no evidence that HF patients were at increased risk for these procedure-related events.

Catheter ablation, as well as surgical MAZE procedures, work by creating scars that block pulmonary vein triggers of AF and in some cases interrupt the reentrant circuits that allow AF to perpetuate. Although the elimination of AF usually improves cardiac performance and clinical outcomes, in theory aggressive or repeated catheter ablation procedures could provoke deterioration in a vulnerable subset by increasing the total amount of atrial fibrosis thereby worsening left atrial compliance.[39] The "stiff left atrial syndrome" complication, marked by symptomatic pulmonary hypertension, has been reported as a rare complication after catheter ablation treatment of AF,[42,43] and extensive scarring of the left atrial has been one proposed mechanism to explain the phenomenon.[44] The need for multiple repeat ablation procedures is believed to be a risk factor, presumably because of cumulative fibrosis burden, although the diagnosis is still largely one of exclusion. No data yet exist to indicate that HF patients are at higher risk for this complication.

Limitations

Our results should be considered in light of several important limitations. First, for the purpose of this study, HF was defined phenotypically by the enrolling clinicians (NYHA class II or III symptoms), and we did not require confirmatory diagnostic testing. Without measurement of left ventricular filling pressures, however, the diagnosis of HF still depends largely on clinical judgment. The core clinical features are effort intolerance and symptoms of dyspnea and fatigue with activity. As shown in Table II in the Data Supplement, in our study cohort the NYHA classification was quite concordant with levels of patient-reported physical functional impairments and symptoms of dyspnea and fatigue. Second, we did not require baseline echocardiography to define EF in all subjects. These data were available in ≈75% of patients. Using the subset of data with complete EF, as well as the full HF cohort with imputed EF when missing, did not suggest any clear variation in all-cause mortality benefit from ablation according to status of left ventricular function. These results are concordant with previous observational studies that suggest similar relative clinical benefits in phenotypic HF regardless of baseline EF. Third, in patients who had a baseline EF measured, only 9% had value <40%. Supporting the classification of most of these HF patients as having HF with preserved left ventricular function, hypertension or left ventricular hypertrophy was present at baseline in 92%. Thus, our estimates of the treatment effects of ablation in AF patients with HF address a different part of the HF spectrum from earlier randomized ablation trials, such as CASTLE-AF. Last, ablation had a quantitatively greater effect on overall mortality than on CV mortality or HF hospital admissions. Too few HF deaths occurred in CABANA to assess a treatment effect. Replication in a larger sample is required to determine the clinical significance of these patterns.

CONCLUSIONS

In CABANA AF patients with clinically defined HF, ablation provided clinically important reductions in mortality and recurrent AF and improved QoL relative to drug therapy. These results, in a cohort with predominantly preserved LV function, complement and extend recent trial results showing survival and QoL benefits of ablation in HF subjects with reduced LV function. If these findings can be confirmed in adequately sized replication trials, clinicians would have a powerful new strategy for reducing the patient suffering and premature mortality that result when AF and HF occur together.

ARTICLE INFORMATION

Received August 20, 2020; accepted December 14, 2020.

The Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.120.050991.

Correspondence

Douglas L. Packer, MD, Mayo Clinic Hospital, St. Mary's Campus, 1216 2nd Street SW, Al 2-416, Rochester, MN 55902. Email packer@mayo.edu

Affiliations

Mayo Clinic Hospital, St. Marys Campus, Rochester, MN (D.L.P., K.H.M., P.A.N.). Duke Clinical Research Institute, Duke University, Durham, NC (J.P.P., H.R.A.-K., A.P.S., T.D.B., K.L.L., D.B.M.). University of Washington Medical Center, Seattle (J.E.P.).

Sources of Funding

This study was funded by the National Institutes of Health ([NIH] grants U01HL89709, U01HL089786, U01HL089907, and U01HL089645), St. Jude Medical Foundation and Corporation, Biosense Webster Inc, Medtronic, Inc, and Boston Scientific Corporation.

Disclosures

Dr Packer reports grants from the NIH/National Heart, Lung, and Blood Institute (NHLBI), St. Jude Medical Corporation and Foundation, Biosense Webster, Inc, Medtronic Corp, and Boston Scientific Corp during the conduct of the study; grants from Abbott, Biosense Webster, Inc, Boston Scientific Corp, CardioFocus, Medtronic, Inc, St. Jude Medical, CardioInsight, NIH, Siemens, Thermedical, Endosense, Robertson Foundation, and Hansen Medical; advisory board without compensation from Abbott, Biosense Webster, Inc, Boston Scientific Corp, CardioFocus, Medtronic, Inc, St. Jude Medical, Spectrum Dynamics, Siemens, Thermedical, Johnson & Johnson, and SigNum Preemptive Healthcare, Inc; speaking with honorarium from Biotronik and MediaSphere Medical, LLC; and royalties from Wiley & Sons, Oxford, and St. Jude Medical. Dr Packer and Mayo Clinic jointly have equity in a privately held company, External Beam Ablation Medical Devices, outside the submitted work. In addition, Dr Packer has mapping technologies with royalties paid. Dr Piccini reports grants from ARCA Biopharma, Boston Scientific, Gilead Sciences, Janssen Pharmaceuticals, Abbott, and Verily; consulting from Allergan, Bayer, Johnson & Johnson, Medtronic, Sanofi, and Philips outside the submitted work. Ms Monahan reports grants from NIH/NHLBI, St. Jude Foundation and Corporation, Biosense Webster, Inc., Medtronic, Inc, and Boston Scientific Corp, during the conduct of the study; consulting without compensation from Biosense Webster, Inc; and personal fees from Thermedical outside the submitted work. Dr Al-Khalidi reports grants from the NIH/NHLBI and Mayo Clinic during the conduct of the study. Dr Noseworthy reports grants from NHLBI outside the submitted work. Dr Poole reports grants from ATriCure outside the submitted work. Dr Bahnson reports grants from the NIH/NHLBI and Mayo Clinic during the conduct of the study; grants from St. Jude Medical, Inc, Abbott Medical, Biosense Webster Inc, Johnson & Johnson, NIH, and Boston Scientific, Corp; and consulting from Cardiofocus, Inc, and Ventrix outside the submitted work. Dr Lee reports grants from the NIH/NHLBI and Mayo Clinic, as well as Data Safety Monitoring Board service on studies funded by Astra-Zeneca, Medtronic, Merck, Amgen, and the Cardiovascular Research Foundation during the conduct of the study. Dr Mark reports grants from NIH/NHLBI and Mayo Clinic during the conduct of the study; grants from Merck, Oxygen Therapeutics, Bristol Myers Squibb, Astra Zeneca, University of Calgary, Eli Lilly & Company, AGA Medical, St. Jude Medical, and Tufts University; and personal fees from CeleCor outside the submitted work. The other author reports no conflicts.

Supplemental Materials

Data Supplement Figures I–IV
Data Supplement Tables I–IV

REFERENCES

1. Skanes AC, Tang ASL. Atrial fibrillation and heart failure: untangling a modern Gordian Knot. *Can J Cardiol.* 2018;34:1437-1448. doi: 10.1016/j.cjca.2018.07.483
2. Nguyen BO, Rienstra M, Hobbelt AH, Tijssen JGP, Smit MD, Tieleman RG, Geelhoed B, Van Veldhuisen DJ, Crijns HJGM, Van Gelder IC; RACE 3 Investigators. Optimal treatment of underlying conditions improves rhythm control outcome in atrial fibrillation: data from RACE 3. *Am Heart J.* 2020;226:235–239. doi: 10.1016/j.ahj.2019.12.005
3. AlTurki A, Proietti R, Dawas A, Alturki H, Huynh T, Essebag V. Catheter ablation for atrial fibrillation in heart failure with reduced ejection fraction: a systematic review and meta-analysis of randomized controlled trials. *BMC Cardiovasc Disord.* 2019;19:18. doi: 10.1186/s12872-019-0998-2
4. Di Biase L, Mohanty P, Mohanty S, Santangeli P, Trivedi C, Lakkireddy D, Reddy M, Jais P, Themistoclakis S, Dello Russo A, et al. Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the AATAC multicenter randomized trial. *Circulation.* 2016;133:1637–1644. doi: 10.1161/CIRCULATIONAHA.115.019406
5. Hunter RJ, Berriman TJ, Diab I, Kamdar R, Richmond L, Baker V, Goromonzi F, Sawhney V, Duncan E, Page SP, et al. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). *Circ Arrhythm Electrophysiol.* 2014;7:31–38. doi: 10.1161/CIRCEP.113.000806
6. Jones DG, Haldar SK, Hussain W, Sharma R, Francis DP, Rahman-Haley SL, McDonagh TA, Underwood SR, Markides V, Wong T. A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. *J Am Coll Cardiol.* 2013;61:1894–1903. doi: 10.1016/j.jacc.2013.01.069
7. Kuck KH, Merkely B, Zahn R, Arentz T, Seidl K, Schluter M, Tilz RR, Piorkowski C, Geller L, Kleemann T, et al. Catheter ablation versus best medical therapy in patients with persistent atrial fibrillation and congestive heart failure: the randomized AMICA trial. *Circ Arrhythm Electrophysiol.* 2019;12:e007731. doi: 10.1161/CIRCEP.119.007731
8. MacDonald MR, Connelly DT, Hawkins NM, Steedman T, Payne J, Shaw M, Denvir M, Bhagra S, Small S, Martin W, et al. Radiofrequency ablation for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a randomised controlled trial. *Heart.* 2011;97:740–747. doi: 10.1136/hrt.2010.207340
9. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P, Proff J, et al; CASTLE-AF Investigators. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med.* 2018;378:417–427. doi: 10.1056/NEJMoa1707855
10. Prabhu S, Taylor AJ, Costello BT, Kaye DM, McLellan AJA, Voskoboinik A, Sugumar H, Lockwood SM, Stokes MB, Pathik B, et al. Catheter ablation versus medical rate control in atrial fibrillation and systolic dysfunction: the CAMERA-MRI Study. *J Am Coll Cardiol.* 2017;70:1949–1961. doi: 10.1016/j.jacc.2017.08.041
11. Turagam MK, Garg J, Sartori S, Dukkipati SR, Reddy VY. Catheter ablation of atrial fibrillation in patients with heart failure. *Ann Intern Med.* 2019;171:76–77. doi: 10.7326/L19-0282
12. Black-Maier E, Ren X, Steinberg BA, Green CL, Barnett AS, Rosa NS, Al-Khatib SM, Atwater BD, Daubert JP, Frazier-Mills C, et al. Catheter ablation of atrial fibrillation in patients with heart failure and preserved ejection fraction. *Heart Rhythm.* 2018;15:651–657. doi: 10.1016/j.hrthm.2017.12.001
13. Cha YM, Wokhlu A, Asirvatham SJ, Shen WK, Friedman PA, Munger TM, Oh JK, Monahan KH, Haroldson JM, Hodge DO, et al. Success of ablation for atrial fibrillation in isolated left ventricular diastolic dysfunction: a comparison to systolic dysfunction and normal ventricular function. *Circ Arrhythm Electrophysiol.* 2011;4:724–732. doi: 10.1161/CIRCEP.110.960690
14. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Poole JE, Noseworthy PA, Rosenberg YD, Jeffries N, Mitchell LB, et al; CABANA Investigators. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA.* 2019;321:1261–1274. doi: 10.1001/jama.2019.0693
15. Mark DB, Anstrom KJ, Sheng S, Piccini JP, Baloch KN, Monahan KH, Daniels MR, Bahnson TD, Poole JE, Rosenberg Y, et al; CABANA Investigators. Effect of catheter ablation vs medical therapy on quality of life among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA.* 2019;321:1275–1285. doi: 10.1001/jama.2019.0692
16. Poole JE, Bahnson TD, Monahan KH, Johnson G, Rostami H, Silverstein AP, Al-Khalidi HR, Rosenberg Y, Mark DB, Lee KL, et al. Recurrence of atrial fibrillation after catheter ablation or antiarrhythmic drug therapy in the CABANA trial. *J Am Coll Cardiol.* 2020;75:3105-3118. doi: 10.1016/j.jacc.2020.04.065
17. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Moretz K, Poole JE, Mascette A, Rosenberg Y, Jeffries N, et al; CABANA Investigators. Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) Trial: study rationale and design. *Am Heart J.* 2018;199:192–199. doi: 10.1016/j.ahj.2018.02.015
18. Spertus J, Dorian P, Bubien R, Lewis S, Godejohn D, Reynolds MR, Lakkireddy DR, Wimmer AP, Bhandari A, Burk C. Development and validation of the Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT) questionnaire in patients with atrial fibrillation. *Circ Arrhythm Electrophysiol.* 2011;4:15–25. doi: 10.1161/CIRCEP.110.958033
19. Bubien RS, Knotts-Dolson SM, Plumb VJ, Kay GN. Effect of radiofrequency catheter ablation on health-related quality of life and activities of daily living in patients with recurrent arrhythmias. *Circulation.* 1996;94:1585–1591. doi: 10.1161/01.cir.94.7.1585
20. Wokhlu A, Monahan KH, Hodge DO, Asirvatham SJ, Friedman PA, Munger TM, Bradley DJ, Bluhm CM, Haroldson JM, Packer DL. Long-term quality of life after ablation of atrial fibrillation the impact of recurrence, symptom relief, and placebo effect. *J Am Coll Cardiol.* 2010;55:2308–2316. doi: 10.1016/j.jacc.2010.01.040
21. Pfeffer MA, Shah AM, Borlaug BA. Heart failure with preserved ejection fraction in perspective. *Circ Res.* 2019;124:1598–1617. doi: 10.1161/CIRCRESAHA.119.313572
22. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Statistical Assoc.* 1958:457–481.
23. Cox D. Regression models and life-tables (with discussion). *J Royal Statist Soc B.* 1972;34:187–220.

24. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Statistical Assoc.* 1999;94:496–509.
25. Mark DB, Lee KL, Harrell FE Jr. Understanding the role of P values and hypothesis tests in clinical research. *JAMA Cardiol.* 2016;1:1048–1054. doi: 10.1001/jamacardio.2016.3312
26. Wood AM, White IR, Royston P. How should variable selection be performed with multiply imputed data? *Stat Med.* 2008;27:3227–3246. doi: 10.1002/sim.3177
27. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: executive summary. *Heart Rhythm.* 2017;14:e445–e494. doi: 10.1016/j.hrthm.2017.07.009
28. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P; ESC Committee for Practice Guidelines (CPG). 2012 Focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation–developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J.* 2012;33:2719–2747. doi: 10.1093/eurheartj/ehs253
29. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA III, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, et al; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; Heart Rhythm Society. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation.* 2013;127:e283–e352. doi: 10.1161/CIR.0b013e318276ce9b
30. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, et al; ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology–developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2012;33:1787–1847. doi: 10.1093/eurheartj/ehs104
31. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Jr., Ellinor PT, Ezekowitz MD, Field ME, Furie KL, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Heart Rhythm*. 2019;16:e66-e93. doi: 10.1016/j.hrthm.2019.01.024
32. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation.* 1998;98:946–952. doi: 10.1161/01.cir.98.10.946
33. Miyasaka Y, Barnes ME, Bailey KR, Cha SS, Gersh BJ, Seward JB, Tsang TS. Mortality trends in patients diagnosed with first atrial fibrillation: a 21-year community-based study. *J Am Coll Cardiol.* 2007;49:986–992. doi: 10.1016/j.jacc.2006.10.062
34. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med.* 2002;113:359–364. doi: 10.1016/s0002-9343(02)01236-6
35. Vidaillet H, Granada JF, Chyou Po, Maassen K, Ortiz M, Pulido JN, Sharma P, Smith PN, Hayes J. A population-based study of mortality among patients with atrial fibrillation or flutter. *Am J Med.* 2002;113:365–370. doi: 10.1016/s0002-9343(02)01253-6
36. Andersson T, Magnuson A, Bryngelsson IL, Frobert O, Henriksson KM, Edvardsson N, Poci D. All-cause mortality in 272,186 patients hospitalized with incident atrial fibrillation 1995-2008: a Swedish nationwide long-term case-control study. *Eur Heart J.* 2013;34:1061-1067. doi: 10.1093/eurheartj/ehs469
37. Bassand JP, Accetta G, Camm AJ, Cools F, Fitzmaurice DA, Fox KA, Goldhaber SZ, Goto S, Haas S, Hacke W, et al; GARFIELD-AF Investigators. Two-year outcomes of patients with newly diagnosed atrial fibrillation: results from GARFIELD-AF. *Eur Heart J.* 2016;37:2882–2889. doi: 10.1093/eurheartj/ehw233
38. Conen D, Chae CU, Glynn RJ, Tedrow UB, Everett BM, Buring JE, Albert CM. Risk of death and cardiovascular events in initially healthy women with new-onset atrial fibrillation. *JAMA.* 2011;305:2080–2087. doi: 10.1001/jama.2011.659
39. Packer M. Effect of catheter ablation on pre-existing abnormalities of left atrial systolic, diastolic, and neurohormonal functions in patients with chronic heart failure and atrial fibrillation. *Eur Heart J.* 2019;40:1873-1879. doi: 10.1093/eurheartj/ehz284.
40. Patel RB, Vaduganathan M, Shah SJ, Butler J. Atrial fibrillation in heart failure with preserved ejection fraction: insights into mechanisms and therapeutics. *Pharmacol Ther.* 2017;176:32–39. doi: 10.1016/j.pharmthera.2016.10.019
41. Noseworthy PA, Gersh BJ, Kent DM, Piccini JP, Packer DL, Shah ND, Yao X. Atrial fibrillation ablation in practice: assessing CABANA generalizability. *Eur Heart J.* 2019;40:1257–1264. doi: 10.1093/eurheartj/ehz085
42. Gibson DN, Di Biase L, Mohanty P, Patel JD, Bai R, Sanchez J, Burkhardt JD, Heywood JT, Johnson AD, Rubenson DS, et al. Stiff left atrial syndrome after catheter ablation for atrial fibrillation: clinical characterization, prevalence, and predictors. *Heart Rhythm.* 2011;8:1364–1371. doi: 10.1016/j.hrthm.2011.02.026
43. Reddy YNV, El Sabbagh A, Packer D, Nishimura RA. Evaluation of shortness of breath after atrial fibrillation ablation-Is there a stiff left atrium? *Heart Rhythm.* 2018;15:930–935. doi: 10.1016/j.hrthm.2018.01.029
44. Witt CM, Fenstad ER, Cha YM, Kane GC, Kushwaha SS, Hodge DO, Asirvatham SJ, Oh JK, Packer DL, Powell BD. Increase in pulmonary arterial pressure after atrial fibrillation ablation: incidence and associated findings. *J Interv Card Electrophysiol.* 2014;40:47–52. doi: 10.1007/s10840-014-9875-1