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Early Rhythm Control Therapy in Patients with Atrial Fibrillation and Heart Failure

Running Title: *Rillig, et al.; Early Rhythm Control in Patients with Heart Failure*

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Abstract

Background: Even on optimal therapy, many patients with heart failure and atrial fibrillation experience cardiovascular complications. Additional treatments are needed to reduce these events, especially in patients with heart failure and preserved left ventricular ejection fraction (HFpEF).

Methods: This prespecified subanalysis of the randomized EAST – AFNET 4 trial assessed the effect of systematic, early rhythm control therapy (ERC; using antiarrhythmic drugs or catheter ablation) compared to usual care (UC, allowing rhythm control therapy to improve symptoms) on the two primary outcomes of the trial and on selected secondary outcomes in patients with heart failure, defined as heart failure symptoms NYHA II-III or left ventricular ejection fraction [LVEF] <50%.

Results: This analysis included 798 patients (300 (37.6%) female, median age 71.0 [64.0, 76.0] years, 785 with known LVEF). The majority of patients (n=442) had HFpEF (LVEF≥50%; mean LVEF 61% ± 6.3%), the others had heart failure with mid-range ejection fraction (n=211; LVEF40-49%; mean LVEF 44% ± 2.9%) or heart failure with reduced ejection fraction (n=132; LVEF<40%; mean LVEF 31% ± 5.5%). Over the 5.1-year median follow-up, the composite primary outcome of cardiovascular death, stroke or hospitalization for worsening of heart failure or for acute coronary syndrome occurred less often in patients randomized to ERC (94/396; 5.7 per 100 patient-years) compared with patients randomized to UC (130/402; 7.9 per 100 patient-years; hazard ratio 0.74 [0.56-0.97], p=0.03), not altered by heart failure status (interaction p-value=0.63). The primary safety outcome (death, stroke, or serious adverse events related to rhythm control therapy) occurred in 71/396 (17.9%) heart failure patients randomized to ERC and in 87/402 (21.6%) heart failure patients randomized to UC (hazard ratio 0.85 [0.62-1.17], p=0.33). LV ejection fraction improved in both groups (LVEF change at two years: ERC 5.3%±11.6%, UC 4.9%±11.6%, p=0.43). ERC also improved the composite outcome of death or hospitalization for worsening of heart failure.

Conclusions: Rhythm control therapy conveys clinical benefit when initiated within one year of diagnosing atrial fibrillation in patients with signs or symptoms of heart failure.

Clinical Trial Registration: Unique Identifiers: ISRCTN04708680, NCT01288352, EudraCT2010-021258-20, Study web site www.easttrial.org; URLs: www.controlled-trials.com; https://clinicaltrials.gov; https://www.clinicaltrialsregister.eu

Key Words: atrial fibrillation; rhythm control; controlled trial; heart failure; atrial fibrillation ablation; antiarrhythmic drugs; stroke; cardiovascular death; acute coronary syndrome

Non-standard Abbreviations and Acronyms

EAST – AFNET4	Early treatment of atrial fibrillation for stroke prevention trial
ERC	Early rhythm control
HFpEF	Heart Failure with preserved ejection fraction
HFmEF	Heart Failure with mid-range ejection fraction
HFrEF	Heart Failure with reduced ejection fraction
UC	Usual Care

Clinical Perspective

What is new?

- This prespecified subanalysis of the randomized EAST-AFNET 4 trial demonstrates that systematic, early rhythm control therapy using antiarrhythmic drugs and atrial fibrillation ablation is safe and reduces cardiovascular outcomes in patients with atrial fibrillation and heart failure compared with the current strategy of delayed, symptom-directed rhythm control.
- The clinical benefit of early rhythm control therapy was observed in patients with preserved, mid-range and reduced left ventricular ejection fraction.
- Early rhythm control therapy was delivered using a combination of antiarrhythmic drugs and AF ablation within guideline recommendations.
- Left ventricular function, symptoms, and quality of life improved equally in both treatment strategies.

What are the clinical implications?

- Our study supports a treatment strategy of rhythm control therapy (with antiarrhythmic drugs or AF ablation) within a year of diagnosing atrial fibrillation in patients with signs or symptoms of heart failure to reduce cardiovascular outcomes.

Introduction

Atrial fibrillation and heart failure are two associated, common cardiovascular diseases.[1] Approximately 30% of patients with atrial fibrillation also have heart failure.[2-4] The sequence of presentation varies, but patients with both conditions are at particular risk of cardiovascular complications,[5, 6] including all-cause and cardiovascular death,[5, 7] stroke, and worsening of heart failure[8] across the spectrum of left ventricular functions.[7, 8] Several smaller studies evaluated whether rhythm control therapy using atrial fibrillation ablation can improve outcomes in patients with atrial fibrillation and heart failure with severely reduced ejection fraction, providing homogeneous data demonstrating improved left ventricular function[9, 10] and a signal for better outcomes.[11] These findings led to an increased use of rhythm control therapy, often atrial fibrillation ablation, in patients with heart failure and reduced ejection fraction.[12,13] Whereas the majority of these trials used catheter ablation to deliver rhythm control therapy, the EAST – AFNET 4 trial recently demonstrated a clinical benefit of early rhythm control therapy using a combination of antiarrhythmic drugs and atrial fibrillation ablation.[14] It is less clear whether rhythm control therapy conveys clinical benefit in patients with moderately reduced or preserved left ventricular ejection fraction.[15] Whether the clinical benefit of the EAST-AFNET4 trial can be transferred to patients with stable heart failure, especially patients with HFpEF, and whether the beneficial effects found using atrial fibrillation ablation in patients with reduced ejection fraction can be replicated by early rhythm control using either antiarrhythmic drugs or atrial fibrillation ablation, is not known.

Methods

The Early Treatment for Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET4) was

conducted as an international, investigator-initiated, parallel-group, randomized, open, blinded outcome-assessment trial.[16] Access to the data will be made available upon request. Please contact info@kompetenznetz-vorhofflimmern.de. The EAST – AFNET4 trial protocol was approved by ethical review boards for all institutions including approval for the analyses outlined in its statistical analysis plan. All participants gave informed consent.

Trial population and trial intervention

The EAST-AFNET4 trial enrolled adults with early atrial fibrillation, defined as atrial fibrillation diagnosed ≤ 12 months before enrollment. For inclusion, patients were required to be either older than 75 years of age, had a previous transient ischemic attack or stroke or met two of the following criteria: age > 65 years, female sex, heart failure, hypertension, diabetes mellitus, severe coronary artery disease, chronic kidney disease (Modification of Diet in Renal Disease stage 3 or 4 [glomerular filtration rate 15 - 59 ml /1.73 m^2 of body-surface area][16]), and left ventricular hypertrophy (diastolic septal wall width, >15 mm). Overall, 2789 patients were randomized in a 1:1 fashion to be treated by early rhythm control (n=1395) or usual care (n=1394).[14] In the early rhythm control group, antiarrhythmic drug therapy, atrial fibrillation ablation or cardioversion were required to be initiated early after randomization.

In patients randomized to usual care the initial treatment consisted of rate-control therapy without rhythm-control therapy. Rhythm-control was used only for symptom-restricted rhythm control therapy, that is, to treat uncontrolled atrial fibrillation–related symptoms despite adequate rate-control.[14]

Heart failure subgroup analysis and outcomes

For this pre-specified subgroup analysis, all patients with signs or symptoms of heart failure at enrolment into the EAST-AFNET4 trial[14, 16] were analyzed. Heart failure and/or asymptomatic

left ventricular dysfunction were defined as symptoms according to NYHA class II-III and/or left ventricular ejection fraction <50%. Patients were stratified according to baseline left ventricular ejection fraction into patients with reduced ejection fraction (HFrEF, left ventricular ejection fraction <40%), moderately reduced ejection fraction (HFmrEF, left ventricular ejection fraction 40-49%) and preserved ejection fraction (HFpEF, left ventricular ejection fraction ≥50%). The effects of early rhythm control and usual care between randomized groups [intention to treat (ITT analysis)] were compared in patients with heart failure as a whole and categorized by left ventricular function. Effects on the first primary outcome (composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome), the second primary outcome (number of nights spent in the hospital per year), and key secondary outcomes (heart rhythm, left ventricular ejection fraction, quality of life, atrial fibrillation related symptoms and cognitive function) of the EAST-AFNET4 trial[14] were analyzed. Furthermore, the primary safety outcome, a composite of death from any cause, stroke, or prespecified serious adverse events was evaluated.

In addition, a "CASTLE-AF like" outcome of death or hospitalization for worsening of heart failure according to the primary outcome of the CASTLE-AF trial[11] as well as a "CABANA-like" composite outcome of death, disabling stroke, serious bleeding or cardiac arrest according to the outcome of the CABANA trial[17] were analyzed. Both were calculated using the correlating defined outcomes of the EAST-AFNET4 trial as assessed by the EAST-AFNET4 endpoint review committee[14].

Statistical analyses

Baseline characteristics of patients are summarized with descriptive statistical methods.

Continuous variables are described by mean and standard deviation or median, 1st and 3rd quantile. Categorical data are summarized as absolute and relative frequencies.

The first primary and second primary outcomes of the overall EAST-AFNET4 trial were pre-specified for this analysis. For the analysis of the first primary outcome, a Cox proportional hazards model with a frailty, i.e. gamma distributed random effect, for the cluster center was applied. This model was also used for the analysis of further time-to-event outcomes, i.e. time to cardiovascular death, time to first stroke, time to first hospitalization for worsening heart failure, time to first hospitalization for acute coronary syndrome, time to all-cause death, time to the primary safety outcome, a composite of all-cause death and hospitalization for worsening heart failure, as well as a composite of all-cause death, major bleeding, or ischemic stroke with a Rankin Score ≥2. The Aalen-Johansen estimator for estimating cumulative incidences was used to account for the competing event "all-cause death" within the primary outcome analysis. Kaplan-Meier based cumulative incidences were used if all-cause death was a component of the outcome.

The second primary outcome was calculated as the observed sum of nights in the hospital divided by the individual follow-up time (in days; in the case of a follow-up time of 0 days, 0.01 days of follow-up was assumed) and was analyzed using a mixed negative binomial model. This model was also used for the analyses of number of hospitalizations.

Baseline-adjusted mixed linear models were used for continuous secondary outcomes, i.e. left ventricular ejection fraction change (baseline to 24 month), change in EQ-5D, change in SF-12 (Mental and Physical Score), change in Montreal Cognitive Assessment (MoCA) score. A random intercept for center was assumed and REML method was used.

Sinus rhythm and symptoms at 24 months were analyzed using mixed logistic models. Ordered logistic mixed models were used to analyze improvement in EHRA score and NYHA class from baseline to 24 months.

To analyze whether catheter ablation had an impact on time-to-event outcomes, a time-varying covariate was used for catheter ablation, i.e. the group changed if catheter ablation was observed prior to the first event within the primary outcome. The same holds for other outcomes, where only the ablation is counted that was observed before the outcome.

Safety outcomes were analyzed via chi square test. Multivariable regression was applied to gain adjusted effects. An interaction term between treatment group and heart failure was considered in the models.

Subgroup analysis was conducted in the same manner as for the first primary outcome but additionally included a corresponding interaction term between treatment group and subgroup of interest. Analysis for multivariable models and secondary outcomes within linear or (ordered) logistic models are based on multiple imputed baseline data with 60 imputations to replace missing values for continuous outcomes and covariates defined for adjustment (see more details in the main paper/supplement of the main paper).[14] All effects, i.e. mean differences or ratios, are given with corresponding 95% confidence intervals. Due to the explorative design of the study no adjustment for multiple testing was conducted, i.e. p-values are descriptive. Statistic software R Version 4.0.3. was used.

Results

EAST-AFNET4 randomized 798 patients with stable heart failure, including 442 (56.3%) patients with HFpEF, 211 (26.9%) patients with HFmrEF, and 132 (16.8%) patients with HFrEF.

Baseline left ventricular ejection fraction was missing in 13 patients and imputed for the analysis (Figure 1). Patient characteristics were not different between randomized groups (Table 1). Patient characteristics as per left ventricular ejection fraction subgroup are listed in Table 1 and Supplementary Table I. Follow-up was available in all patients. The primary outcome occurred in 94/396 patients randomized to early rhythm control and in 130/402 patients randomized to usual care (univariable hazard ratio (HR) 0.74 [95% CI 0.56, 0.97], p=0.03; Table 2 and Figure 2): The effect was not different to the treatment effect in patients with normal left ventricular function and without signs of heart failure (HR 0.81 [0.66, 1.01], p=0.06; interaction p (between treatment and heart failure)=0.63). Patients with and without ischemic cardiomyopathy had a similar risk for the first primary and the second primary outcome; also, changes in left ventricular function occurred with comparable incidence for both groups (Supplementary Table II). Patients with preserved left ventricular ejection fraction had a lower risk for the first primary outcome compared with patients with reduced left ventricular ejection fraction (reduced vs preserved HR 1.76 [1.19, 2.59]). Patients with preserved and mid-range left ventricular ejection fraction had a similar risk for the first primary outcome (mid-range vs preserved HR 1.01 [0.68, 1.50]). Total nights spent in hospital were higher in patients randomized to early rhythm control compared with usual care (8.36±27.85 versus 7.46±23.9, univariable treatment effect 1.28 [1.01, 1.62]; p=0.04; Table 2; Supplementary Figure I; for non-heart failure: 1.00 [0.86, 1.17]; p=0.96; interaction p=0.11). Secondary outcomes were observed as depicted in Table 2. Subgroup analysis is shown in Supplementary Figure II.

Outcomes based on the CASTLE-AF and CABANA trials

Early rhythm control also improved a combined outcome of death or hospitalization for worsening of heart failure: Ninety-one/396 patients randomized to early rhythm control

experienced a combined outcome of death or hospitalization for worsening of heart failure compared with 123/402 patients with events in those randomized to usual care (p=0.04; Supplementary Figure III; treatment group-HF interaction p=0.49). The composite outcome of death, disabling stroke, serious bleeding or cardiac arrest was numerically lower in patients randomized to early rhythm control (51/396 patients with event) than in those randomized to usual care (71/402 patients with event), without significant inter-group difference (p=0.10; Supplementary Table III and Figure IV; treatment group-HF interaction p=0.32).

Rhythm control therapy

Rhythm control therapy was initiated in the majority of patients (367/391, 93.9%), Figure 1) randomized to early rhythm control and was prescribed only in a minority of patients in the usual control arm (23/394, 5.8%, Figure 1) at randomization. The difference remained substantial after 2 years (early rhythm control 252/351, 71.8%; usual care 69/352, 19.6%, Figure 1). Most patients randomized to early rhythm control received flecainide, dronedarone or amiodarone (Figure 1 and Supplementary Table IV). Sinus rhythm at baseline was recorded more often in patients with early rhythm control than in patients with usual care (Table 1) and was not associated with better outcome for both primary outcomes within multivariable analysis. Based on resting-ECG evaluation at 12 and 24 months, sinus rhythm was observed more often in the early rhythm control group (Supplementary Figure V). Catheter ablation was performed in 140 patients with heart failure including 88 patients randomized to early rhythm control and 52 patients randomized to usual care. Characteristics and distribution of patients treated with or without catheter ablation are shown in Supplementary Table V and Figure VI. The effect of early rhythm control did not differ between patients treated with atrial fibrillation ablation and patients treated with antiarrhythmic drugs. Visual inspection identified a slight (non-significant) early

excess of first primary outcomes in the subgroup of patients with HFpEF. The tabulated outcomes suggest numerically more early heart failure events in patients treated with amiodarone (Table 3).

Safety outcome

There were no significant differences between early rhythm control and usual care for the primary safety outcome (Table 4 and Supplementary Table VI).

Improvement of left ventricular ejection fraction

Left ventricular ejection fraction improved in both groups, resulting in similar improvement of left ventricular ejection fraction in patients randomized to early rhythm control or to usual care (mean improvement in left ventricular ejection fraction 5.3%±11.6 vs. 4.9%±11.6, respectively; univariable p=0.43; Table 2; interaction p-value (between treatment group and HF)=0.38). Left ventricular ejection fraction improved mainly in patients with reduced or mid-range left ventricular ejection fraction (Figure 3 and Supplementary Figure VII) without differences between randomized groups. A complete recovery of initially reduced left ventricular ejection fraction was observed in 24 patients randomized to early rhythm control and in 26 patients randomized to usual care, whereas an increase of left ventricular ejection fraction above the recommended threshold for ICD-implantation (35%) occurred in 24 patients of the early rhythm control group and in 29 patients treated with usual care (Supplementary Table VII). Sensitivity analysis using only complete cases did not show significant differences when compared with imputed data (mean improvement in left ventricular ejection fraction early rhythm control 5.6%±11.7; usual care 4.4%±11.5; univariable p=0.24; Supplementary Table VIII)

Symptoms and quality of life

At the end of the follow-up, a similar number of patients without atrial fibrillation-related symptoms were seen in the early rhythm control and the usual care arm (early rhythm control 226 (69.54%), usual care 214 (64.65%)) and similar outcomes regarding quality of life (EQ-5D early rhythm control -2.2±24.3 vs. usual care -4.3±25.6) were observed (Table 2). Atrial fibrillation symptoms improved at 24 months in both randomized groups (early rhythm control 56.4%; usual care 54.2%, Supplementary Table IX and X) without inter-group differences.

Anticoagulation and heart failure therapy

The vast majority of patients (around 90%) received guideline-recommended oral anticoagulation throughout the follow-up without differences between both groups. Vitamin-K-antagonists and the novel oral anticoagulants were evenly distributed (Supplementary Table XI). Therapy of concomitant cardiovascular conditions appeared well balanced, and a normal blood pressure throughout follow-up was seen in both groups (Supplementary Figure VIII). Heart failure medication did not show differences between randomized groups at discharge, including high use of betablockers (79.1%; early rhythm control 78.4%, usual care 79.9%), ACE or angiotensin II receptor blockers (62.5%; early rhythm control 60.1%, usual care 64.9%) or diuretics (50.4%; early rhythm control 49.7%, usual care 51.0%, Supplementary Table XII and XIII). Mineral corticoid receptor antagonist use was not as high as recommended, but similar between randomized groups (overall 12.4 %; early rhythm control 13.7%; usual care 11.2%) Digitalis glycoside use at discharge was higher in the usual care group (usual care 9.7%; early rhythm control 5.8%), but was not associated with worse outcomes (Supplementary Table XIV and XV).

Rate control therapy

Rate control therapy as the mainstay of usual care was initiated in 366 patients resulting in a well-controlled median heart rate of 65.5 beats/min. in the usual care group. Importantly, rate control therapy was given in addition to rhythm control in 85.1% (337) of patients randomized to early rhythm control, mainly using betablockers (78.4%) (Figure 1; Supplementary Table XIII and Table XVI).

Outcomes according to NYHA class

Within multivariable analysis, NYHA class at baseline showed some association with primary and secondary outcomes, i.e. NYHA II or III compared with asymptomatic heart failure. NYHA classes II and III were not related to left ventricular ejection fraction changes (Supplementary Figure XVI). Changes in NYHA class for patients with early rhythm control and usual care are visualized in Figure 3. Heart failure symptoms estimated by NYHA class improved after 24 months in both groups (early rhythm control 53.2%, usual care 45.3%) with a slightly higher improvement in patients randomized to early rhythm control (p=0.05; Table 2). The highest improvement in NYHA class occurred in patients with preserved ejection fraction (Supplementary Table VII).

Multivariable analysis

Adjusted effects associated with the first primary outcome were observed for sex (female vs. male HR 0.65 (0.47 to 0.89), ejection fraction (reduced left ventricular ejection fraction vs. preserved left ventricular ejection fraction HR 1.76 (1.48 to 2.10) and NYHA class II (NYHA class II vs. no heart failure HR 2.31 (1.31 to 4.07), and NYHA class III (NYHA class III vs. no heart failure HR 3.93 (2.09 to 7.39)).

Complete case analysis

A complete case analysis of EAST-AFNET4 heart failure patients for secondary outcomes where imputation was necessary is provided in Supplementary Table XVII.

Discussion

Main findings

This analysis demonstrates, that early rhythm control therapy reduces a composite of cardiovascular death, stroke or hospitalization for worsening of heart failure or for acute coronary syndrome compared with usual care (including rhythm control use to improve AF-related symptoms) in patients with signs or symptoms of heart failure. A similar clinical benefit of early rhythm control was found when a "CASTLE-AF like" outcome was calculated, extending the clinical benefit found in that study to an unselected cohort of heart failure patients with reduced and preserved ejection fraction receiving rhythm control therapy using either antiarrhythmic drugs or AF ablation. Unlike CASTLE-AF, the clinical benefit of early rhythm control was achieved using antiarrhythmic drugs or AF ablation, chosen by the site investigators within guideline recommendations. The majority of patients in this analysis presented with heart failure with preserved ejection fraction, similar to the recently published subanalysis of the CABANA trial comparing catheter ablation and antiarrhythmic drug therapy in patients with atrial fibrillation and heart failure.[18] The clinical benefit of early rhythm control was not associated with improved left ventricular ejection fraction at two years compared with usual care. Strengths of the analysis are the long median follow-up duration of 5.1-years and enrolment of a broad spectrum of patients with heart failure and recently diagnosed atrial fibrillation.

Type of rhythm control therapy

The majority of patients were treated with antiarrhythmic drugs, with amiodarone (in HFrEF[19]), and flecainide, dronedarone or amiodarone (in HFpEF, Figure 1) as the main agents. Antiarrhythmic drugs were prescribed according to the current guidelines and at the recommended dose.[12,13] Approximately 17% of patients randomized to early rhythm control were treated with atrial fibrillation ablation in the first two years after randomization. This suggests that the clinical benefit found in this subanalysis can be achieved using antiarrhythmic drugs as initial therapy. It is worthwhile to note that flecainide was used in a relatively high number of patients without safety concerns. All treatments were given following the guidance of international AF guidelines, potentially enabling the safe use of antiarrhythmic drugs in this population.

As expected, patients treated by early rhythm control were more likely to present in sinus rhythm at the 24 months follow-up when compared with usual care. Also, the proportion of patients with atrial fibrillation at two years was higher in this analysis than in the overall cohort of the EAST-AFNET4 trial. This is in line with previously published data,[20,14] as heart failure is believed to contribute to recurrent atrial fibrillation and to atrial cardiomyopathy[21] in patients with atrial fibrillation.[22] It seems plausible that early initiation of therapy was one of the factors that rendered antiarrhythmic drug therapy relatively effective in this analysis. Catheter ablation of atrial fibrillation improves quality of life and reduces arrhythmia recurrence to a higher extent compared with antiarrhythmic drug therapy, with signals that there may be clinical benefit, especially in patients with reduced left ventricular function.[20, 23-25] In view of the clinical benefit of catheter ablation compared with antiarrhythmic drug therapy seen in the CABANA heart failure subanalysis[18], it is tempting to speculate that early rhythm control using catheter ablation

could convey even larger clinical benefit than the treatment pattern chosen by the investigators of the EAST-AFNET4 trial. Alternatively, antiarrhythmic drugs may be sufficient to achieve early rhythm control therapy due to the lower risk of recurrent atrial fibrillation. The value of catheter ablation for early rhythm control awaits testing in a controlled clinical trial.

Timing of rhythm control therapy

Heart failure patients with atrial fibrillation are at high risk of cardiovascular events including cardiovascular death[5, 7], stroke, and worsening of heart failure.[8] Recent onset atrial fibrillation is associated with worse outcomes than established atrial fibrillation.[26,2] The early timing of rhythm control therapy in this study could have amplified the clinical benefit of early rhythm control compared with usual care. It is also possible that the early initiation of rhythm control therapy led to an improved efficacy of antiarrhythmic drug therapy as compared with other trials testing antiarrhythmic drugs for rhythm control therapy in patients with heart failure.[18, 19]

Role of left ventricular function

Patients with preserved left ventricular ejection fraction had a lower risk for the first primary outcome compared with patients with reduced left ventricular ejection fraction. This is in line with the findings of several previous studies on patients with reduced ejection fraction and points to the fact that left ventricular function retains prognostic importance in patients with heart failure and atrial fibrillation.[20,23,25] Reduction of cardiovascular events by heart failure therapies such as inhibitors of the renin-angiotensin-aldosterone system or cardiac resynchronization therapy is accompanied by improvements of cardiac function in patients with heart failure and reduced ejection fraction. Early studies found that catheter ablation can improve left ventricular function in patients with atrial fibrillation and tachycardiomyopathy.[27] The findings of the CASTLE-AF trial corroborate this theory, as catheter ablation in heart failure patients with atrial

fibrillation resulted not only in better outcomes of the death from any cause or hospitalization for worsening heart failure but also in a clinically relevant improvement of left ventricular function.[20] The present analysis showed a similar clinical benefit of early rhythm control therapy which was not accompanied by improved left ventricular ejection fraction at two years compared with usual care. It is possible that rhythm control therapy given to symptomatic patients with heart failure and atrial fibrillation led to improved left ventricular function in patients randomized to usual care. Exploratory analyses suggest that treatment with amiodarone, but not treatment with flecainide, propafenone or dronedarone, was potentially associated with early heart failure hospitalizations in patients with heart failure and preserved left ventricular function. This is unexpected as amiodarone is considered a safe antiarrhythmic drug in patients with heart failure [13,28,29,30] and calls for further clinical research to determine the optimal antiarrhythmic drug therapy in patients with heart failure and preserved ejection fraction.

In summary, this analysis suggests that early rhythm control can prevent clinical outcomes in patients with heart failure and that left ventricular function remains a predictor of outcomes in patients with heart failure and atrial fibrillation. In addition, sinus rhythm was not associated with better primary outcomes. This might at least in part be explained by the fact that rhythm control therapy was allowed when symptoms or signs of tachycardiomyopathy occurred in the usual care group.

Heart failure therapy and anticoagulation therapy

Heart failure patients in the EAST-AFNET4 trial were medically well-treated in both study arms, without differences between randomized groups. Treatment included a high use of recommended heart failure therapies with betablockers, ACE inhibitors or angiotensin-II receptor antagonists. Mineralocorticoid antagonists were prescribed less often, but with no difference between

randomized groups. In accordance to the recommendations for heart failure treatment valid at the time of recruitment and earlier follow-up period, only a few patients received ARNI, and there was no use of SGLT2 inhibitors. These novel drugs for heart failure have shown additional benefits including reduced outcomes and improved left ventricular ejection fraction [31,32], yet are unlikely to interact with the intervention of the EAST-AFNET4 trial.

Over 90% of patients with atrial fibrillation and heart failure received oral anticoagulation without differences between randomized groups. The majority of patients were treated with NOACs. This implicates that oral anticoagulation as a confounder on relevant clinical outcomes such as stroke or cardiovascular mortality is unlikely.

Rate control therapy

Rate control therapy was delivered as recommended by current guidelines.[12,13] Most patients in both randomized groups received rate control therapy. The proportion of patients treated with selective rate controlling medication was higher in the patients randomized to usual care. When the rate controlling effects of antiarrhythmic drugs (amiodarone, dronedarone, propafenone) is considered, this difference is smaller. While we cannot exclude a theoretical effect on outcomes associated with a more intensive rate control therapy, this is unlikely, in view of the neutral outcome of the RACE II trial.[33] Besides rate controlling effects of antiarrhythmic drugs, the high use of betablocker therapy as a standard of care in heart failure patients explains the high rate of prescription of rate controlling therapy in the early rhythm control group.

Safety aspects

Both, antiarrhythmic drug therapy and catheter ablation in patients with heart failure and atrial fibrillation were evenly safe in this analysis, supporting the main findings of the EAST-AFNET 4 trial.

Limitations and strengths

This analysis was prespecified in the statistical analysis plan of the EAST-AFNET 4 trial, but the trial was not powered specifically for this subanalysis. EAST-AFNET4 is a strategy trial, the intervention was not blinded, and there are no data on left ventricular function or quality of life beyond two years of follow-up. Despite these limitations, this analysis reports the first contemporary comparison of systematic early rhythm control therapy compared with restricted and delayed rhythm control in patients with atrial fibrillation and heart failure. The size of the population is larger than most randomized trials published so far, and very comparable to the heart failure subanalysis of CABANA. A strength of the analysis is the control group receiving treatment according to contemporary atrial fibrillation guidelines.

Conclusions

This subanalysis of the EAST – AFNET 4 trial demonstrates that early rhythm control therapy using antiarrhythmic drugs or atrial fibrillation ablation is safe and reduces cardiovascular events in patients with heart failure. The clinical benefit of early rhythm control is not associated with greater improvement in left ventricular ejection fraction compared to that observed with usual care. Clinical benefit is observed across the spectrum of heart failure subtypes, suggesting that restoring and maintaining sinus rhythm via rhythm control therapy conveys the clinical benefit. In the view of the authors, all patients with signs or symptoms of heart failure should be considered for rhythm control therapy within a year of being diagnosed with atrial fibrillation.

Supplemental Material

Further data is available in the online data supplement

Supplemental Tables I – XVII

Supplemental Figures I - IX

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Disclosures

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Table 1. Clinical characteristics of the EAST-AFNET4 heart failure patients at baseline by randomized groups.

	Early rhythm control (N=396)	Usual care (N=402)	Total (N=798)
Left ventricular ejection fraction at baseline categories			
missing variables	5	8	13
reduced	57 (14.6%)	75 (19.0%)	132 (16.8%)
mid-range	110 (28.1%)	101 (25.6%)	211 (26.9%)
preserved	224 (57.3%)	218 (55.3%)	442 (56.3%)
Left ventricular ejection fraction at baseline 2 categories			
missing variables	5	8	13
<35	35 (9.0%)	47 (11.9%)	82 (10.4%)
>=35	356 (91.0%)	347 (88.1%)	703 (89.6%)
Left ventricular ejection fraction at baseline			
missing variables	5	8	13
means and standard deviation	51.8 (12.4)	50.9 (13.0)	51.4 (12.7)
Median (Q1, Q3)	52.0 (44.5, 62.0)	52.0 (41.2, 61.0)	52.0 (43.0, 62.0)
range	13.0 - 82.0	18.0 - 85.0	13.0 - 85.0
Sex			
Male	240 (60.6%)	258 (64.2%)	498 (62.4%)
Female	156 (39.4%)	144 (35.8%)	300 (37.6%)
Age			
means and standard deviation	69.5 (9.3)	70.4 (9.0)	69.9 (9.2)
Median (Q1, Q3)	70.5 (63.8, 76.0)	72.0 (65.0, 77.0)	71.0 (64.0, 76.0)
range	39.0 - 90.0	34.0 - 91.0	34.0 - 91.0
Body Mass Index (calculated) [kg/m^2]			
missing variables	2	1	3
means and standard deviation	29.9 (6.1)	30.1 (5.6)	30.0 (5.9)
Median (Q1, Q3)	29.1 (26.1, 32.8)	29.4 (26.2, 33.3)	29.4 (26.2, 33.2)
range	16.6 - 58.2	18.1 - 53.3	16.6 - 58.2
Cardiomyopathy			
missing variables	2	0	2
No	310 (78.7%)	337 (83.8%)	647 (81.3%)
Tachycardiomyopathy	25 (6.3%)	12 (3.0%)	37 (4.6%)
Hypertrophic cardiomyopathy	4 (1.0%)	3 (0.7%)	7 (0.9%)
Dilatative cardiomyopathy	24 (6.1%)	29 (7.2%)	53 (6.7%)
Other cardiomyopathy	22 (5.6%)	14 (3.5%)	36 (4.5%)
Unknown	9 (2.3%)	7 (1.7%)	16 (2.0%)
Severe coronary artery disease (previous myocardial infarction, CABG or PCI)			
No	308 (77.8%)	311 (77.4%)	619 (77.6%)
Yes	88 (22.2%)	91 (22.6%)	179 (22.4%)
Atrial fibrillation type			
missing variables	2	0	2
First episode	136 (34.5%)	146 (36.3%)	282 (35.4%)
Paroxysmal	131 (33.2%)	121 (30.1%)	252 (31.7%)
Persistent or long-standing persistent	127 (32.2%)	135 (33.6%)	262 (32.9%)

Duration of atrial fibrillation history at baseline (days)			
missing variables	1	0	1
means and standard deviation	73.6 (96.5)	79.4 (176.4)	76.5 (142.5)
Median (Q1, Q3)	31.0 (6.0, 109.0)	24.5 (5.0, 99.8)	27.0 (5.0, 102.0)
range	0.0 - 639.0	0.0 - 2310.0	0.0 - 2310.0
CHA_2DS_2-Vasc Score			
means and standard deviation	4.0 (1.4)	4.0 (1.4)	4.0 (1.4)
Median (Q1, Q3)	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)
range	1.0 - 8.0	1.0 - 9.0	1.0 - 9.0
Overall symptom score (EHRA)			
missing variables	37	23	60
EHRA I (asymptomatic)	81 (22.6%)	88 (23.2%)	169 (22.9%)
EHRA II	183 (51.0%)	213 (56.2%)	396 (53.7%)
EHRA III	93 (25.9%)	75 (19.8%)	168 (22.8%)
EHRA IV	2 (0.6%)	3 (0.8%)	5 (0.7%)
Heart failure (NYHA classification)			
missing variables	2	0	2
No heart failure	39 (9.9%)	55 (13.7%)	94 (11.8%)
I	35 (8.9%)	33 (8.2%)	68 (8.5%)
II	255 (64.7%)	259 (64.4%)	514 (64.6%)
III	65 (16.5%)	55 (13.7%)	120 (15.1%)
Prior stroke or transient ischemic attack			
No	354 (89.4%)	355 (88.3%)	709 (88.8%)
Yes	42 (10.6%)	47 (11.7%)	89 (11.2%)
Arterial hypertension			
No	44 (11.1%)	58 (14.4%)	102 (12.8%)
Yes	352 (88.9%)	344 (85.6%)	696 (87.2%)
No	333 (84.1%)	332 (82.6%)	665 (83.3%)
Yes	63 (15.9%)	70 (17.4%)	133 (16.7%)
Heart rhythm			
missing variables	2	0	2
Atrial fibrillation or atrial flutter	217 (55.1%)	237 (59.0%)	454 (57.0%)
Sinus rhythm and pacing	177 (44.9%)	165 (41.0%)	342 (43.0%)
Left ventricular hypertrophy on echocardiography (> 15mm wall thickness)			
No	384 (97.0%)	388 (96.5%)	772 (96.7%)
Yes	12 (3.0%)	14 (3.5%)	26 (3.3%)
Systolic LA diameter (maximal diameter) [mm]			
missing variables	342	349	691
means and standard deviation	42.1 (13.9)	43.2 (15.3)	42.6 (14.5)
Median (Q1, Q3)	43.0 (38.0, 48.8)	43.0 (38.0, 52.0)	43.0 (38.0, 49.5)
Range	0.0 - 71.0	0.0 - 74.0	0.0 - 74.0
Diastolic LA diameter (maximal diameter) [mm]			
missing variables	77	86	163
means and standard deviation	45.4 (8.0)	46.0 (9.1)	45.7 (8.5)
Median (Q1, Q3)	44.0 (40.0, 50.0)	44.0 (40.0, 50.0)	44.0 (40.0, 50.0)

Range	26.0 - 74.0	28.0 - 85.0	26.0 - 85.0
Fractional shortening (calculated) [%]			
missing variables	88	98	186
means and standard deviation	28.0 (9.9)	29.1 (10.4)	28.5 (10.2)
Median (Q1, Q3)	27.5 (21.0, 35.0)	29.0 (22.0, 36.0)	28.0 (21.0, 36.0)
Range	5.0 - 67.0	6.0 - 80.0	5.0 - 80.0
Diabetes			
missing variables	2	0	2
No diabetes or imp. glucose tolerance	281 (71.3%)	300 (74.6%)	581 (73.0%)
Yes (managed by diet, oral antidiabetics, and/or insulin or no therapy)	113 (28.7%)	102 (25.4%)	215 (27.0%)

No clinical characteristics presented in this table demonstrated a statistically significant difference between early rhythm control or usual care. Left ventricular function was assessed using two-dimensional quantification based on the Simpson method. Left atrial size was determined in M mode. CABG Coronary artery bypass graft; PCI Percutaneous coronary intervention; CHA2DS2-VASc score conducted with Congestive Heart failure; EHRA score European Heart Rhythm Association score for assessment of atrial fibrillation symptoms; NYHA class New York Heart Association classification of symptoms in heart failure patients; LA Left atrium.

Table 2. Outcomes of early rhythm control and usual care in patients with heart failure.

Outcome	Early rhythm control n=396	Usual care n=402	Treatment effect	p-value	interaction p-value (treatment group and HF)
First primary outcome patients with events/person-years (incidence/100 person-years)	94/1649 (5.7)	130/1650 (7.9)	0.74 (0.56 to 0.97)	0.03	0.63
Death from cardiovascular causes	26/1848 (1.4)	49/1911 (2.6)	0.54 (0.33 to 0.87)	0.011	0.13
Stroke	8/1827 (0.4)	18/1874 (1.0)	0.46 (0.20 to 1.05)	0.07	0.36
Hospitalization for worsening of heart failure	66/1705 (3.9)	81/1706 (4.7)	0.82 (0.59 to 1.14)	0.24	0.91
Hospitalization for acute coronary syndrome	15/1802 (0.8)	17/1858 (0.9)	0.92 (0.46 to 1.85)	0.83	0.70
All-cause death	47/1848 (2.5)	65/1911 (3.4)	0.74 (0.50 to 1.08)	0.11	0.39
All-cause death or Hospitalization for worsening of heart failure ("CASTLE-AF like outcome")	91/1705 (5.3)	123/1706 (7.2)	0.74 (0.56 to 0.98)	0.04	0.49
Second primary outcome - nights spent in hospital/yr	8.36±27.85	7.46±23.90	1.28 (1.01 to 1.62)	0.04	0.11
Number of hospitalizations/yr	0.96±1.14	0.99±1.44	0.99 (0.76 to 1.19)	0.86	0.74
Change in left ventricular ejection fraction from baseline to 24 months	5.3±11.6	4.9±11.6	0.57 (-0.84 to 1.98)	0.43	0.54
Change in EQ-5D score (24 months)	-2.2±24.3	-4.3±25.6	1.89 (-1.76 to 5.54)	0.31	0.59
Change in SF-12 Mental Score (24 months)	0.2±11.5	2.0±10.8	-1.29 (-2.98 to 0.39)	0.13	0.90
Change in SF-12 Physical Score (24 months)	0.6±8.7	-0.0±9.4	0.21 (-1.16 to 1.59)	0.76	0.81
Change in MoCA score (24 months)	-0.1±3.3	0.2±3.3	-0.21 (-0.70 to 0.28)	0.41	0.69
Sinus rhythm at 24 months— no. of patients with feature/total no. (%)	246/313 (78.59)	175/320 (54.69)	2.97 (2.09 to 4.23)	<0.001	0.86
Asymptomatic at 24 months— no. of patients with feature/total no. (%)	226/325 (69.54)	214/331 (64.65)	1.36 (0.93 to 1.99)	0.17	0.37
Digoxin at 24 months	12/325 (3.69)	32/331 (9.67)	0.41 (0.20 to 0.84)	0.016	0.85
NYHA Improved	173/325 (53.2)	150/331 (45.3)	p-value mixed ordered logistic regression 0.05		0.24
NYHA Unchanged	117/325 (36.0)	142/331 (42.9)			
NYHA Worsened	35/325 (10.8)	39/331 (11.8)			

Primary and secondary outcomes observed in patients with heart failure enrolled in the EAST-AFNET4 trial by randomized groups. Efficacy outcomes and changes of left ventricular function and NYHA class of the EAST-AFNET4 heart failure population by randomized groups. EAST-AFNET4 indicates Early Treatment for Atrial Fibrillation for Stroke Prevention Trial. NYHA class New York Heart Association classification of symptoms in heart failure patients. EQ-5D score European Quality of Life 5 Dimensions score; SF-12 Short Form Health survey 12-items; MoCA score Montreal Cognitive Assessment Score.

Table 3. Exploratory analysis of primary outcomes within 12 months after randomization in patients randomized to early rhythm control, split by planned initial rhythm therapy.

	Planned rhythm control at baseline in patients randomized to early rhythm control					
	AF Ablation	**Dronedarone**	**Amiodarone**	**Flecainide or Propefanone**	**Other antiarrhythmic drug**	**All patients**
Patients with moderately or severely reduced left ventricular function	3/14 (21.4%)	2/19 (10.5%)	10/81 (12.3%)	0/31 (0.0%)	0/11 (0.0%)	15/156 (9.0%)
Patients with preserved left ventricular function	1/17 (5.9%)	1/20 (5.0%)	8/42 (19.0%)	8/122 (6.6%)	1/10 (10.0%)	20/211 (8.9%)

The choice of initial rhythm control therapy did not affect early outcomes significantly (p-value for difference in time to first primary outcome between planned initial rhythm control therapy p=0.20). Numbers give patients with events / patients in the groups (percentage of patients with events).

Table 4. Safety outcomes in the EAST-AFNET4 heart failure study population by randomized groups.

	Early rhythm control (N=396)	Usual care (N=402)	Total (N=798)	p value
Occurrence of a primary safety outcome	71 (17.9%)	87 (21.6%)	158 (19.8%)	0.19
Occurrence of stroke	8 (2.0%)	18 (4.5%)	26 (3.3%)	0.05
Occurrence of cardiovascular death	26 (6.6%)	49 (12.2%)	75 (9.4%)	0.006
Occurrence of death	47 (11.9%)	65 (16.2%)	112 (14.0%)	0.08
Occurrence of a SAE of special interest	20 (5.1%)	10 (2.5%)	30 (3.8%)	0.06
Occurrence of a SAE of special interest type arrhythmia	12 (3.0%)	6 (1.5%)	18 (2.3%)	0.14
Occurrence of a SAE of special interest type other	9 (2.3%)	6 (1.5%)	15 (1.9%)	0.42

Safety outcomes did not differ between randomized groups (results of chi-square test). Numerically there were less events observed in the early rhythm control group. SAE Severe adverse event as defined within the EAST-AFNET4 main manuscript [14]. EAST-AFNET4 indicates Early Treatment for Atrial Fibrillation for Stroke Prevention Trial.

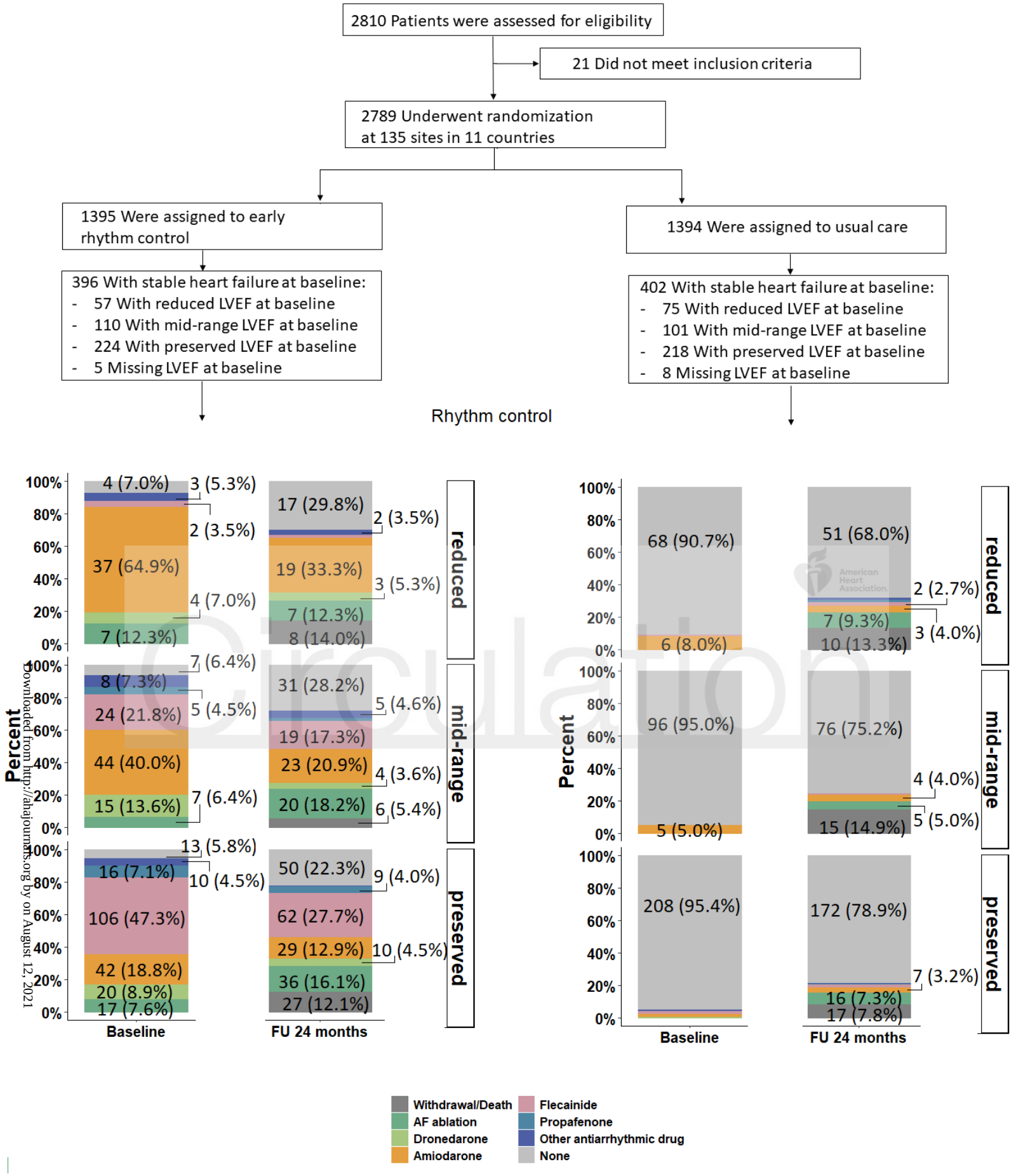
Figure Legends

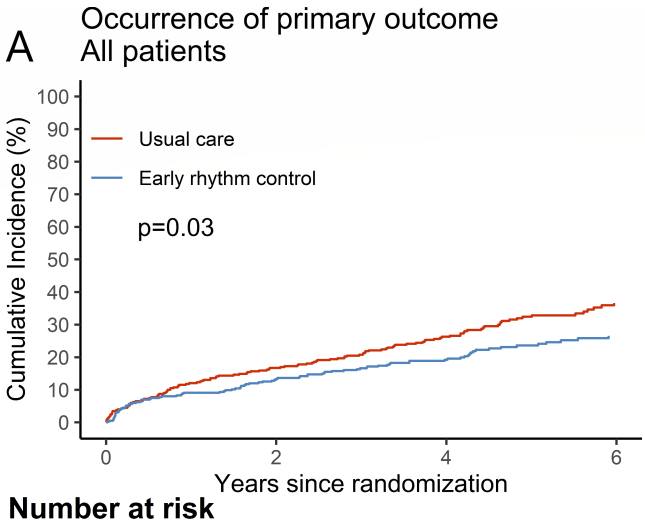
Figure 1. Consort flow chart of the EAST-AFNET4 heart failure subanalysis. A total of 798 patients with heart failure were included in this analysis, 396 randomized to early rhythm control and 402 randomized to usual care. During follow-up, in the early rhythm control group 201/2049 total follow-up years were lost (147 follow-up years lost because 31 patients withdrew; 54 follow-up years lost because 36 patients were lost to follow-up) and 159/2070 total follow-up years were lost in the usual care group (108 follow-up years lost because 26 patients withdrew; 51 follow-up years lost because 33 patients were lost to follow-up). LVEF Left ventricular ejection fraction. Screening and randomization are replicated from the main paper.[14]

Figure 2. Primary outcome in EAST-AFNET4 heart failure patients by randomized groups. Aalen-Johansen Cumulative-Incidence Curves for the effects of early rhythm control on the primary outcome. Primary outcome defined as a composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome. **A:** All patients with heart failure. **B:** Heart failure with reduced ejection fraction. **C:** Heart failure with mid-range ejection fraction. **D:** Heart failure with preserved ejection fraction. HFpEF Heart failure with preserved ejection fraction; HFmEF Heart failure with mid-range ejection fraction; HFrEF Heart failure with reduced ejection fraction.

Figure 3. Left ventricular function and changes in left ventricular function of EAST-AFNET4 heart failure patients by randomized groups. Changes in left ventricular ejection fraction between baseline and two years are given in the overall heart failure population (all

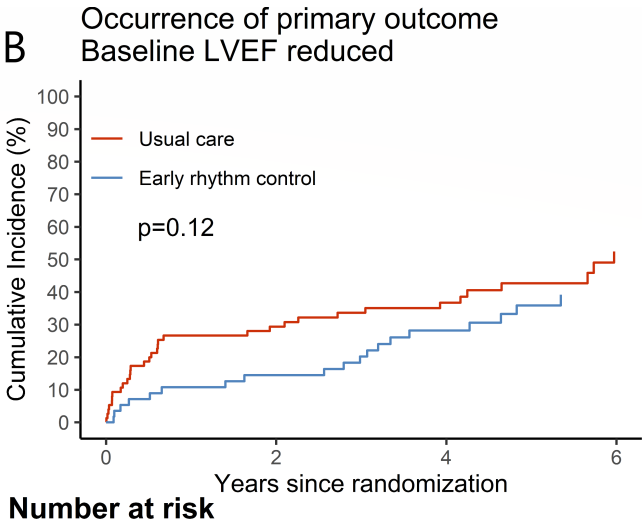
patients, left) and split by left ventricular ejection fraction groups (reduced, mid-range, and preserved). The numerical changes in LVEF, split by randomized group, were early rhythm control, reduced LVEF 17.28±13.45; usual care, reduced LVEF 18.10±10.73, mean difference -0.83 (-4.44 to 2.79, p=0.66); early rhythm control, mid-range LVEF 9.25±10.44; usual care, mid-range LVEF 8.68±8.97 (mean difference 0.66 (-1.99 to 3.31), p=0.63); early rhythm control, preserved LVEF 0.33±8.33; usual care, preserved LVEF -0.93±8.34 (mean difference 0.98 (-0.83 to 2.79), p=0.29. LVEF Left ventricular ejection fraction.





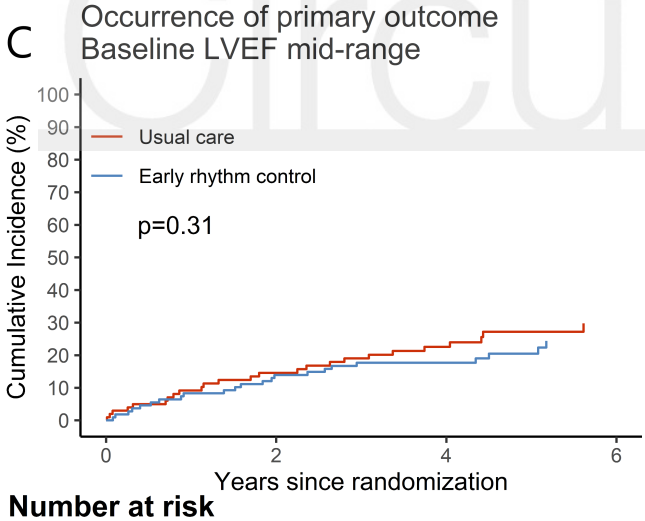
Number at risk

Usual care	402	315	223	91
Early rhythm control	396	316	226	92



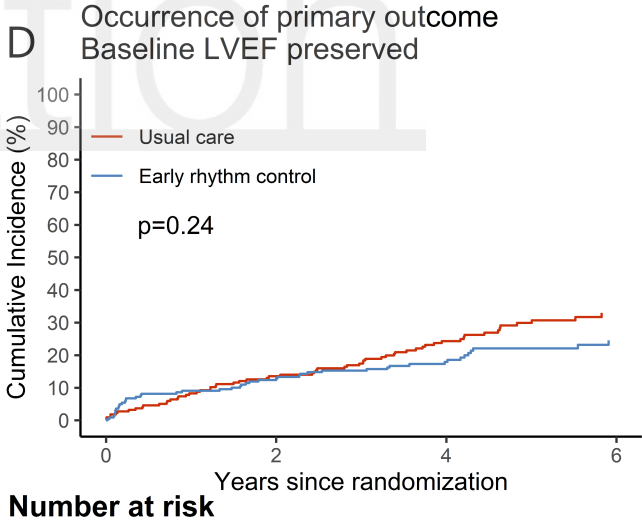
Number at risk

Usual care	75	51	36	13
Early rhythm control	57	43	29	14



Number at risk

Usual care	101	78	56	25
Early rhythm control	110	91	70	26



Number at risk

Usual care	218	180	126	51
Early rhythm control	224	180	126	51