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FASTTRACK **CLINICAL RESEARCH**
Arrhythmias

Systematic, early rhythm control strategy for atrial fibrillation in patients with or without symptoms: the EAST-AFNET 4 trial

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See the editorial comment for this article 'Rhythm control in asymptomatic 'early' atrial fibrillation: birth of a new paradigm?', by Robert Hatala, https://doi.org/10.1093/eurheartj/ehab811.

Aims	Clinical practice guidelines restrict rhythm control therapy to patients with symptomatic atrial fibrillation (AF). The EAST-AFNET 4 trial demonstrated that early, systematic rhythm control improves clinical outcomes compared to symptom-directed rhythm control.
Methods and results	This prespecified EAST-AFNET 4 analysis compared the effect of early rhythm control therapy in asymptomatic patients (EHRA score I) to symptomatic patients. Primary outcome was a composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome, analyzed in a time-to-event analysis. At baseline, 801/2633 (30.4%) patients were asymptomatic [mean age 71.3 years, 37.5% women, mean CHA_2DS_2-VASc score 3.4, 169/801 (21.1%) heart failure]. Asymptomatic patients randomized to early rhythm control (395/801) received similar rhythm control therapies compared to symptomatic patients [e.g. AF ablation at 24 months: 75/395 (19.0%) in asymptomatic; 176/910 (19.3%) symptomatic patients, $P = 0.672$]. Anticoagulation and treatment of concomitant cardiovascular conditions was not different between symptomatic and asymptomatic patients. The primary outcome occurred in 79/395 asymptomatic patients randomized to early rhythm control and in 97/406 patients randomized to usual care (hazard ratio 0.76, 95% confidence interval [0.6; 1.03]), almost identical to symptomatic patients. At 24 months follow-up, change in symptom status was not different between randomized groups ($P = 0.19$).

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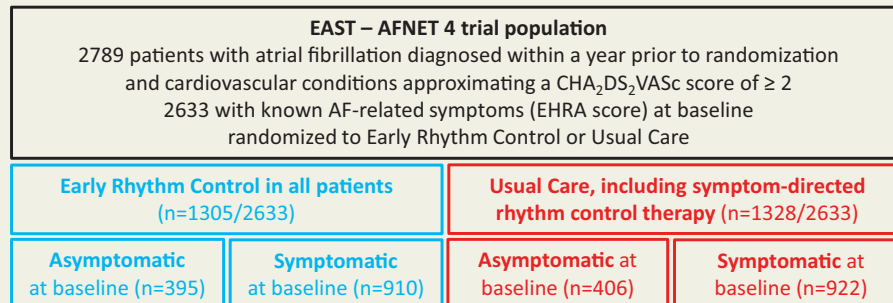| Conclusion	The clinical benefit of early, systematic rhythm control was not different between asymptomatic and symptomatic patients in EAST-AFNET 4. These results call for a shared decision discussing the benefits of rhythm control therapy in all patients with recently diagnosed AF and concomitant cardiovascular conditions (EAST-AFNET 4; ISRCTN04708680; NCT01288352; EudraCT2010-021258-20).

Graphical Abstract

EAST – AFNET 4 trial population
2789 patients with atrial fibrillation diagnosed within a year prior to randomization and cardiovascular conditions approximating a CHA_2DS_2VASc score of ≥ 2
2633 with known AF-related symptoms (EHRA score) at baseline
randomized to Early Rhythm Control or Usual Care

Early Rhythm Control in all patients
(n=1305/2633)

Usual Care, including symptom-directed rhythm control therapy (n=1328/2633)

Asymptomatic at baseline (n=395) | **Symptomatic** at baseline (n=910) | **Asymptomatic** at baseline (n=406) | **Symptomatic** at baseline (n=922)

No difference in treatment pattern between asymptomatic and symptomatic patients.
Excellent symptom control in both randomized groups at two years.

Ca. 1/4 treated with AF ablation and 3/4 treated with antiarrhythmic drugs at 2 years

Ca. 8% treated with AF ablation and 9% treated with antiarrhythmic drugs at 2 years

Similar reduction of cardiovascular death, stroke, or hospitalisation for heart failure or acute coronary syndrome in symptomatic and asymptomatic patients

A asymptomatic at baseline — HR [95% CI]: 0.76 (0.57, 1.03)
B symptomatic at baseline — HR [95% CI]: 0.79 [0.64, 0.98]
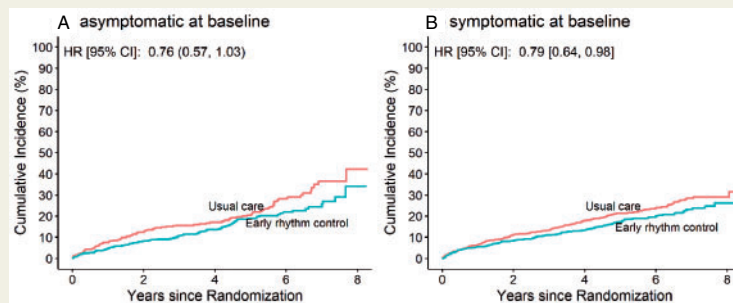
Our findings support the systematic, early initiation of rhythm control therapy in asymptomatic patients with atrial fibrillation and concomitant cardiovascular conditions.

Keywords	Atrial fibrillation • Symptoms • Rhythm control • Ablation • Antiarrhythmic drugs • Clinical trial

Introduction

Atrial fibrillation (AF) remains a major cause of cardiovascular death, stroke, and heart failure even on optimal current management.[1] Approximately 1/3 of unselected patients with AF do not have AF-related symptoms, more often older populations and with persistent forms of AF.[2,3] Asymptomatic AF is associated with similar rates of stroke, cardiovascular death, and other cardiovascular events compared to symptomatic AF.[4–7] Some data suggest that the mortality of asymptomatic patients may even be higher than in symptomatic patients,[4] underscoring the need to better identify and manage asymptomatic patients with AF.

Contemporary AF guidelines recommend anticoagulation and therapy of concomitant cardiovascular conditions in all patients with AF, while rhythm control is restricted to symptomatic patients.[1] However, the EAST-AFNET 4 trial and the earlier ATHENA trial suggest that rhythm control therapy could further reduce cardiovascular events, reporting fewer cardiovascular complications in patients randomized to early rhythm control therapy (EAST-AFNET 4)[8] or to dronedarone (ATHENA).[9] Whether the clinical benefit of

systematic, early rhythm control therapy is present in asymptomatic patients with AF remains to be tested.

Methods

The current analysis was prespecified in the statistical analysis plan and performed on the final, locked database of the EAST-AFNET 4 trial. Design and topline results of the main trial have been published.[8,10] In brief, the EAST-AFNET 4 trial is an international, investigator-initiated, parallel-group, open, blinded- outcome-assessment (PROBE) trial, which randomly assigned patients who had AF diagnosed ≤1 year before enrolment and cardiovascular conditions to receive either early rhythm control in all patients or usual care. Early rhythm control included treatment with antiarrhythmic drugs or AF ablation in all patients directly after randomization. Usual care included rhythm control therapy to improve AF-related symptoms.[8,10]

The current analyses included treatments at discharge from the randomization visit, at one year and at two years of follow-up. Patients were categorized into asymptomatic and symptomatic patients by EHRA score at baseline (asymptomatic = EHRA I; symptomatic = EHRA II–IV). To further explore relations between symptoms and outcomes, patients were classified as asymptomatic (EHRA I), mildly symptomatic (EHRA II), or severely symptomatic (EHRA III or EHRA IV). Patients with missing baseline EHRA scores were excluded.

The effects of early rhythm control therapy were compared between randomized groups (ITT analysis) in patients with different EHRA classes and between asymptomatic and symptomatic patients at baseline. Effects on the primary outcome (composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome, analyzed in a time-to-event analysis) as well as the second primary outcome (number of nights spent in hospital per year) and key secondary outcomes (rhythm, change in symptoms, left ventricular function, quality of life) were analyzed.

Data are presented as mean and standard deviation or number and percentage. To compare data, *P*-values resulting from mixed linear regression models for metric variables and mixed (ordinal) logistic regression models for categorical variables were used where appropriate. Sites were modelled as random effect. For categorical variables with more than two categories (not ordinal), a random effect was not included. Subgroup analyses were conducted with interaction terms.

For the primary outcome and its individual components, we used Cox regression models with an interaction term of treatment group and AF symptom status as well as site as a shared frailty term. The treatment effects are expressed as hazard ratios with 95% confidence interval.

The second primary outcome was analyzed with a mixed negative binomial model with treatment group and AF symptom status as interaction term, the log of follow-up time as offset and site as a random effect. The treatment effect is presented as the incidence rate ratio and 95% confidence interval. The key secondary outcomes at 2 years were analyzed after multiple imputation of missing values in survivors. The multiple-imputation procedure was conducted with 60 imputations for a set of continuous outcomes and covariates for adjustment based on suggestions by White, Royston, and Wood (see statistical analysis plan in the supplement of EAST-AFNET 4).[8] We then calculated a mixed linear model with the corresponding baseline measurement as covariate, a treatment group/AF symptom interaction term and site as a random effect. The treatment effect is expressed as the adjusted mean difference with 95% confidence interval. Data were analyzed using Stata software (StataCorp), version 16.1, and R software, version 4.0.5 (R Project for Statistical Computing).

Results

The study group consisted of 2633 patients randomized across 135 sites in 11 European countries between 28 July 2011 and 30 December 2016. Patients with missing baseline symptom status (156, 2.8%) were not analyzed (*Figure 1*). At baseline, 801/2633 (30.4%) patients were asymptomatic (EHRA score I, mean age 71.3 years, 37.5% women, mean CHA_2DS_2-VASc score 3.4), whereas 1832/2633 (69.6%) patients were symptomatic (*Table 1* and *Supplementary material online, Tables S1 and S2*). The majority of symptomatic patients presented with mild or moderate symptoms (EHRA II, n = 1358, *Table 1*). The mean CHA_2DS_2-VASc score was not different between symptomatic and asymptomatic patients. However, asymptomatic patients were older, less often women, had less heart failure but had higher rates of prior stroke or transient ischaemic attack compared to symptomatic patients (*Table 1*). AF patterns and prior rhythm control therapy also differed. Asymptomatic patients were more often enrolled at their first episode of AF and were less likely to be in paroxysmal AF (*Table 1*). Asymptomatic patients had fewer rhythm control therapy attempts prior to enrolment using antiarrhythmic drugs or electrical or pharmacological cardioversion. Baseline characteristics of asymptomatic patients were well balanced between randomized groups (*Table 1*).

Anticoagulation and treatment of concomitant cardiovascular conditions

Most asymptomatic patients received guideline-adherent oral anticoagulation, comparable to the care in the symptomatic group at baseline [baseline: asymptomatic 723/801 (90.3%), symptomatic 1655/1832 (90.3%)] and during follow-up (*Supplementary material online, Table S2*). Similar to symptomatic patients, treatment of concomitant cardiovascular conditions was well balanced between groups with the exception of slightly lower use of beta-blockers and digitalis glycosides and higher use of statins in asymptomatic patients (*Table 1* and *Supplementary material online, Table S2*, *P* = 0.004, *P* = 0.001, and *P* < 0.001, respectively).

Delivery of early rhythm control and usual care in asymptomatic patients

Of 801 asymptomatic patients, 395 were assigned to early rhythm control and 406 to usual care (*Figure 1*). Rhythm control therapy was initiated in nearly all asymptomatic patients [378/395 (95.7%)] randomized to early rhythm control without difference to symptomatic patients [865/910 (95.1%)] and without effect of symptom status. At the two year follow-up, 242/395 (59.3%) asymptomatic patients were still receiving rhythm control therapy, compared to 601/910 (64.8%) symptomatic patients (*Figure 1* and *Table 2*). Asymptomatic patients randomized to early rhythm control (395/801) received similar rhythm control therapies compared to symptomatic patients. A total of 75/395 (19.0%) asymptomatic patients received AF ablation within 24 months after randomization compared to 176/910 (19.3%) symptomatic patients (*P* = 0.672, *Table 2*). This corresponds to 25% of patients still in follow-up at two years.

Treatment patterns in patients randomized to usual care did not differ between symptomatic and asymptomatic patients. Rate control therapy without rhythm control therapy was given to 390 (96.1%)
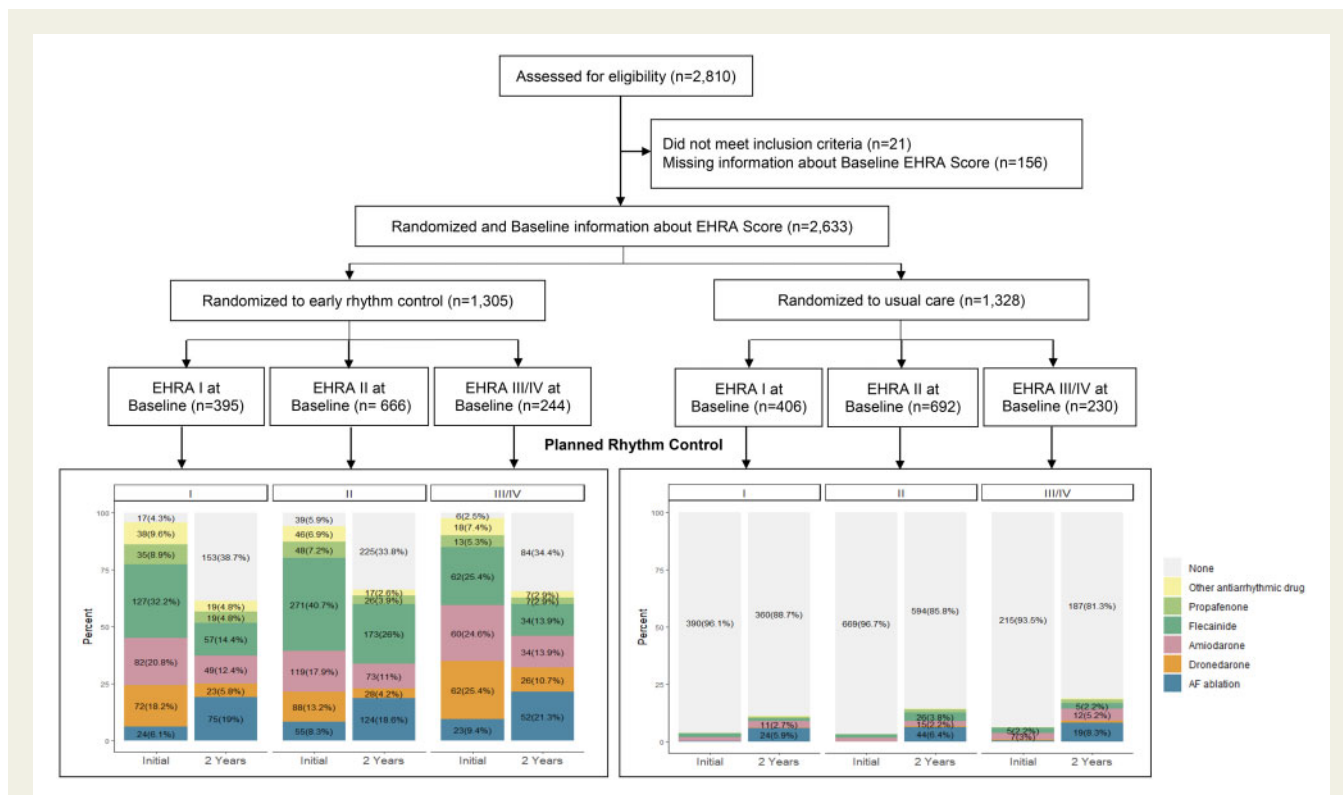
Figure 1 Consort flow chart of the patients included in this analysis showing screening, randomization, treatment, and follow-up. Of all patients included into the EAST-AFNET 4 trial, 21 of the 2810 patients did not meet the inclusion criteria of early atrial fibrillation (diagnosed ≤1 year before enrolment) and cardiovascular conditions. After exclusion of 156 patients with missing baseline symptom status, 2633 patients were included into the analysis with randomization to early rhythm control (*n* = 1305) or usual care (*n* = 1328). Most of the patients assigned to early rhythm-control were initially treated with antiarrhythmic drugs, regardless of symptom status. After 2 years of follow-up, 242 of the 395 asymptomatic patients (59.3%) and 601 of the 910 symptomatic patients (64.8%) who had been randomly assigned to early rhythm control therapy were still receiving active rhythm-control therapy [atrial fibrillation ablation in 75/395 (19.0%) asymptomatic patients and in 176/910 (19.3%) symptomatic patients; *P* = 0.672] randomized to early rhythm control. This corresponds to ca 25% of patients randomized to early rhythm control and still in follow-up at 24 months.

asymptomatic patients randomized to usual care and to 884/922 (95.9%) symptomatic patients. At 2 years, 360/406 patients (89.3%) randomized to usual care were still not receiving rhythm-control therapy, slightly more than in symptomatic patients randomized to usual care [781/922 (85.9%), *P* = 0.0487, *Figure 1* and *Table 2*].

Primary outcome is not different based on symptoms

Death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome (first primary outcome of the trial) occurred in 79/395 asymptomatic patients randomized to early rhythm control, and in 97/406 asymptomatic patients randomized to usual care, with a hazard ratio of 0.76, 95% CI [0.57; 1.03], almost identical to the overall population and to symptomatic patients (*P* = 0.848, *Figure 2* and *Table 3*) and to the outcome in patients with mild to moderate or severe symptoms (*Figure 2* and *Table 3*). The effects of early rhythm control on individual components of the first primary outcome were comparable for

asymptomatic, mildly or moderately symptomatic, and severely symptomatic patients, in line with the overall population (*Table 3*). There was no interaction between symptom status and treatment effect in the primary outcome or any of its components.

Safety outcomes for asymptomatic patients were similar to symptomatic patients with no significant difference between groups (*Table 4*). Mortality and stroke were similar in the two treatment groups. Serious adverse events related to rhythm-control therapy were rare, more common in the group assigned to early rhythm control, and not affected by symptom status.

Effect of early rhythm control therapy on nights spent in hospital and on secondary outcomes in asymptomatic and symptomatic patients

There was no difference in nights spent in hospital per year between asymptomatic, mildly or moderately symptomatic, and severely symptomatic patients (*Table 3*). Furthermore, nights spent in hospital per year were not different between asymptomatic

Table I Demographic and clinical characteristics of the patients at baseline

Characteristics	Overall, N = 2633[a]	Symptom status at baseline (EHRA Class)			P-value[b]
		Asymptomatic (EHRA I), N = 801[a]	Mild or moderate symptoms (EHRA II), N = 1358[a]	Severe symptoms (EHRA III/IV), N = 474[a]	
Age	71 (66.0, 76)	72 (67.0, 77)	71 (65.2, 75)	72 (65.0, 76)	0.003
Female sex	1223/2633 (46%)	300/801 (37%)	629/1358 (46%)	294/474 (62%)	<0.001
Body mass index (calculated) (kg/m^2)	28.6 (25.5, 32.1)	28.4 (25.6, 32.0)	28.3 (25.4, 31.8)	29.4 (25.8, 33.1)	0.047
AF type					<0.001
First episode	1029/2633 (39%)	390/801 (49%)	442/1358 (33%)	197/474 (42%)	
Paroxysmal	901/2633 (34%)	201/801 (25%)	532/1358 (39%)	168/474 (35%)	
Persistent or long-standing persistent	703/2633 (27%)	210/801 (26%)	384/1358 (28%)	109/474 (23%)	
Sinus rhythm at baseline	1424/2632 (54%)	401/800 (50%)	742/1358 (55%)	281/474 (59%)	0.079
Median days since AF diagnosis (IQR)	35.0 (6.0, 110.0)	23.0 (4.0, 86.0)	44.0 (8.0, 124.8)	24.0 (4.0, 103.8)	0.002
Previous pharmacological or electrical cardioversion	1046/2602 (40%)	276/788 (35%)	564/1346 (42%)	206/468 (44%)	<0.001
Concomitant cardiovascular conditions					
Previous stroke or transient ischaemic attack	303/2633 (12%)	116/801 (14%)	140/1358 (10%)	47/474 (9.9%)	0.014
At least mild cognitive impairment	1110/2524 (44%)	383/777 (49%)	514/1309 (39%)	213/438 (49%)	0.007
MoCA score					<0.001
None	1414/2524 (56%)	394/777 (51%)	795/1309 (61%)	225/438 (51%)	
Mild	1016/2524 (40%)	343/777 (44%)	482/1309 (37%)	191/438 (44%)	
Moderate	86/2524 (3.4%)	38/777 (4.9%)	29/1309 (2.2%)	19/438 (4.3%)	
Severe	8/2524 (0.3%)	2/777 (0.3%)	3/1309 (0.2%)	3/438 (0.7%)	
Arterial hypertension	2306/2633 (88%)	693/801 (87%)	1194/1358 (88%)	419/474 (88%)	0.64
Systolic blood pressure (mmHg)	135 (123.0, 150)	137 (123.0, 150)	135 (123.0, 149)	137 (122.0, 150)	0.23
Diastolic blood pressure (mmHg)	80 (73.0, 90)	80 (72.0, 90)	80 (74.0, 90)	80 (70.0, 89)	0.023
Stable heart failure	738/2633 (28%)	169/801 (21%)	396/1358 (29%)	173/474 (36%)	<0.001
CHA$_2$DS$_2$-Vasc score	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (3.0, 4.0)	<0.001
Chronic kidney disease of MDRD stage 3 or 4	337/2633 (13%)	104/801 (13%)	171/1358 (13%)	62/474 (13%)	0.72
Medication at discharge					
Oral anticoagulation with NOAC or VKA	2378/2633 (90%)	723/801 (90%)	1223/1358 (90%)	432/474 (91%)	0.11
Digoxin or digitoxin	129/2633 (4.9%)	24/801 (3.0%)	77/1358 (5.7%)	28/474 (5.9%)	0.003
Beta-blockers	2130/2633 (81%)	624/801 (78%)	1099/1358 (81%)	407/474 (86%)	0.005
ACE inhibitors or angiotensin II receptor blocker	1838/2633 (70%)	580/801 (72%)	929/1358 (68%)	329/474 (69%)	0.41
Mineralocorticoid receptor antagonist	170/2633 (6.5%)	53/801 (6.6%)	88/1358 (6.5%)	29/474 (6.1%)	0.74
Diuretic	1067/2633 (41%)	322/801 (40%)	521/1358 (38%)	224/474 (47%)	0.004
Statin	1139/2633 (43%)	399/801 (50%)	556/1358 (41%)	184/474 (39%)	0.002
Platelet inhibitor	437/2633 (17%)	146/801 (18%)	210/1358 (15%)	81/474 (17%)	0.24
Planned therapy for rhythm control at baseline					0.15
AAD	1193/2633 (45%)	369/801 (46%)	595/1358 (44%)	229/474 (48%)	
Ablation	104/2633 (3.9%)	25/801 (3.1%)	55/1358 (4.1%)	24/474 (5.1%)	
None	1336/2633 (51%)	407/801 (51%)	708/1358 (52%)	221/474 (47%)	

MoCA score categories: none: ≥26; mild: 18–25; moderate: 10–17; severe: <10.
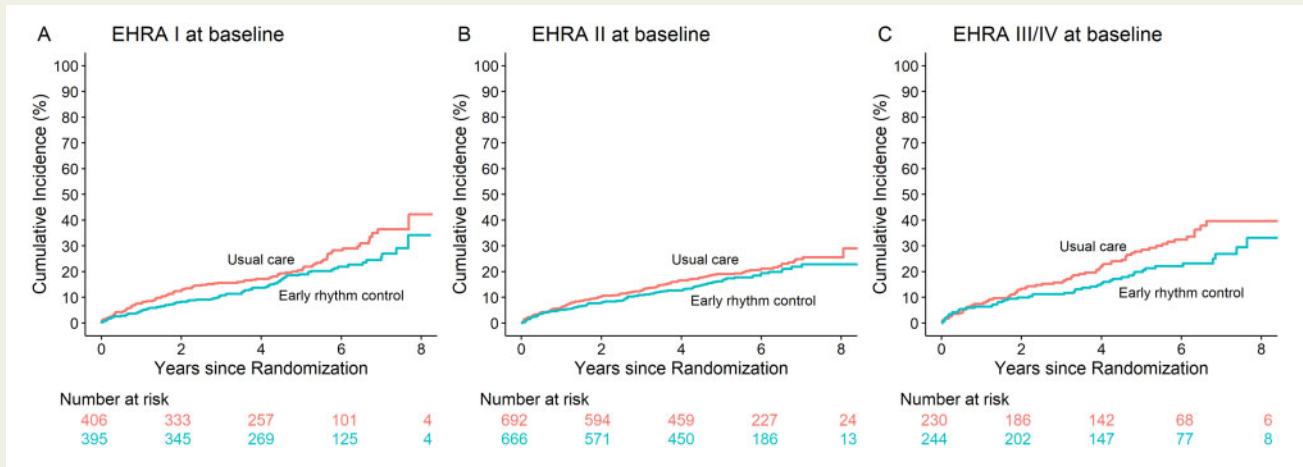
AF, atrial fibrillation.

[a] Median (IQR) or frequency with number/total number (%).

[b] P-values resulting from mixed linear or logistic regression models and Analysis of Deviance Table (Type II Wald chi-square tests). Nominal variables were tested with Pearson's Chi-squared test.

AAD, antiarrhythmic drug; BL, baseline; CI, confidence interval; IQR, interquartile range; HF, heart failure; ITT, intention to treat; MDRD, Modification of Diet in Renal Disease; MoCA, Montréal Cognitive Assessment; NOAC, non vitamin-K-antagonist oral anticoagulant; VKA, vitamin K antagonist.

patients randomized to early rhythm control (5.5 ± 17.9) compared to asymptomatic patients randomized to usual care (6.1 ± 19.2). At 24 months, 255/323 (78.9%) asymptomatic patients in early rhythm control group were in sinus rhythm compared to 170/325 (52.3%) patients in usual care (P < 0.001), similar to the results of symptomatic patients (Table 3). There was no interaction between symptom status and treatment effect in any of the secondary outcomes (Table 3).

Figure 2 Aalen–Johansen cumulative-incidence curves for the first primary outcome: (*A*) for patients with asymptomatic atrial fibrillation at baseline and (*B*) for patients with symptomatic atrial fibrillation at baseline. The first primary outcome was a composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome. The effect of early rhythm control on this outcome was almost identical in symptomatic and asymptomatic patients.

Table 2 Rhythm control planned at baseline and present at 24 months by EHRA score and randomized

	EHRA I		EHRA II		EHRA III/IV	
	Early rhythm control	Usual care	Early rhythm control	Usual care	Early rhythm control	Usual care
n	395	406	666	692	244	230
Rhythm control at BL						
AF ablation	24 (6.1)	1 (0.2)	55 (8.3)	0 (0.0)	23 (9.4)	1 (0.4)
Dronedarone	72 (18.2)	0 (0.0)	88 (13.2)	0 (0.0)	62 (25.4)	1 (0.4)
Amiodarone	82 (20.8)	7 (1.7)	119 (17.9)	12 (1.7)	60 (24.6)	7 (3.0)
Flecainide	127 (32.2)	6 (1.5)	271 (40.7)	10 (1.4)	62 (25.4)	5 (2.2)
Propafenone	35 (8.9)	1 (0.2)	48 (7.2)	1 (0.1)	13 (5.3)	0 (0.0)
Other antiarrhythmic drug	38 (9.6)	1 (0.2)	46 (6.9)	0 (0.0)	18 (7.4)	1 (0.4)
None	17 (4.3)	390 (96.1)	39 (5.9)	669 (96.7)	6 (2.5)	215 (93.5)
Rhythm control at FU24						
AF ablation	75 (19.0)	24 (5.9)	124 (18.6)	44 (6.4)	52 (21.3)	19 (8.3)
Dronedarone	23 (5.8)	1 (0.2)	28 (4.2)	2 (0.3)	26 (10.7)	2 (0.9)
Amiodarone	49 (12.4)	11 (2.7)	73 (11.0)	15 (2.2)	34 (13.9)	12 (5.2)
Flecainide	57 (14.4)	5 (1.2)	173 (26.0)	26 (3.8)	34 (13.9)	5 (2.2)
Propafenone	19 (4.8)	3 (0.7)	26 (3.9)	9 (1.3)	7 (2.9)	4 (1.7)
Other antiarrhythmic drug	19 (4.8)	2 (0.5)	17 (2.6)	2 (0.3)	7 (2.9)	1 (0.4)
None	153 (38.7)	360 (88.7)	225 (33.8)	594 (85.8)	84 (34.4)	187 (81.3)

AF, atrial fibrillation; FU24, 24 months follow-up.

Most patients who were asymptomatic at baseline remained asymptomatic. Only 144/687 (21%) of initially asymptomatic patients became symptomatic in the first 2 years of follow-up, with no difference between randomized groups (*P* = 0.19, Figure 3). In symptomatic patients, AF symptoms decreased over time with 1104/1832 (60.3%) initially symptomatic patients becoming asymptomatic during follow-up.

Discussion

Main findings

This prespecified comparison of the effect of early rhythm control therapy in asymptomatic patients with AF randomized in the EAST-AFNET 4 trial yielded several new findings:

Table 3 Outcomes in the EAST – AFNET 4 trial population by symptom status

Outcome	Asymptomatic (EHRA I)			Mild or moderate symptoms (EHRA II)			Severe symptoms (EHRA III/IV)			P-value interaction
	Early rhythm control	Usual care	Treatment effect	Early rhythm control	Usual care	Treatment effect	Early rhythm control	Usual care	Treatment effect	
First primary outcome	79/1888 (4.2)	97/1774 (5.5)	0.77 (0.57, 1.03)	109/3056 (3.6)	97/1774 (5.5)	0.84 (0.66, 1.09)	49/1099 (4.5)	68/1031 (6.6)	0.68 (0.47, 0.99)	0.743
Components of the first primary outcome										
Death from cardiovascular causes	19/2049 (0.9)	22/1977 (1.1)	0.82 (0.44, 1.52)	30/3277 (0.9)	22/1977 (1.1)	0.73 (0.46, 1.17)	15/1208 (1.2)	22/1189 (1.9)	0.68 (0.35, 1.31)	0.973
Stroke	19/2005 (0.9)	25/1923 (1.3)	0.73 (0.4, 1.33)	14/3242 (0.4)	25/1923 (1.3)	0.7 (0.36, 1.37)	6/1188 (0.5)	12/1151 (1)	0.48 (0.18, 1.27)	0.663
Hospitalization with worsening of heart failure	39/1961 (2)	54/1845 (2.9)	0.67 (0.44, 1.01)	62/3148 (2)	54/1845 (2.9)	0.96 (0.68, 1.35)	31/1141 (2.7)	39/1082 (3.6)	0.76 (0.47, 1.22)	0.432
Hospitalization with acute coronary syndrome	22/2004 (1.1)	18/1929 (0.9)	1.19 (0.64, 2.22)	18/3208 (0.6)	18/1929 (0.9)	0.61 (0.34, 1.09)	10/1180 (0.8)	12/1148 (1)	0.82 (0.35, 1.89)	0.229
Secondary primary outcome—nights spent in hospital/yr	5.5 (17.9)	6.1 (19.2)	0.91 (0.72, 1.16)	5.3 (20.7)	6.1 (19.2)	1.19 (0.99, 1.43)	8.9 (32.4)	5.8 (13.8)	1.19 (0.87, 1.62)	0.193
Key secondary outcomes at 2 years										
Change in left ventricular ejection fraction	0.6 (10.4)	-0.5 (9.8)	0.18 (-1, 1.36)	1.4 (9.4)	-0.5 (9.8)	0.14 (-0.82, 1.1)	3.5 (10.6)	0.9 (11.7)	0.56 (-1.06, 2.17)	0.902
Change in EQ-5D score	1.6 (16.7)	-1.2 (17.2)	1.53 (-1.74, 4.8)	1.1 (16.8)	-1.2 (17.2)	1.31 (-1.26, 3.89)	1.6 (19.6)	4 (19.1)	-0.25 (-4.58, 4.08)	0.797
Change in SF-12 Mental Score	1 (9.7)	1.7 (9.5)	-0.83 (-2.33, 0.68)	0.1 (10.3)	1.7 (9.5)	-1.37 (-2.5, -0.24)	2.6 (12.2)	2.8 (10.9)	-1.3 (-3.3, 0.71)	0.848
Change in SF-12 Physical Score	-0.4 (8.3)	-1.2 (8.4)	0.84 (-0.57, 2.24)	0.5 (8.3)	-1.2 (8.4)	0.02 (-0.96, 1.01)	1.3 (9.1)	1.3 (8.9)	0.39 (-1.3, 2.08)	0.636
Change in MoCA score	0.2 (3.4)	0.1 (3)	0.05 (-0.42, 0.53)	0.1 (3.2)	0.1 (3)	-0.06 (-0.42, 0.3)	-0.1 (3.4)	0.1 (3.1)	-0.66 (-1.31, 0)	0.194
Sinus rhythm	255/323 (78.9)	170/325 (52.3)	3.65 (2.56, 5.22)	450/538 (83.6)	170/325 (52.3)	3.21 (2.41, 4.28)	166/191 (86.9)	141/185 (76.2)	2.12 (1.2, 3.75)	0.287

Table 4 Safety outcomes for EHRA score

	EHRA I		EHRA II		EHRA III/IV	
	Early rhythm control	Usual care	Early rhythm control	Usual care	Early rhythm control	Usual care
n	395	406	666	692	244	230
Primary composite safety outcome	79 (20.0)	63 (15.5)	99 (14.9)	105 (15.2)	44 (18.0)	43 (18.7)
Stroke	19 (4.8)	25 (6.2)	14 (2.1)	22 (3.2)	6 (2.5)	12 (5.2)
Death	45 (11.4)	40 (9.9)	59 (8.9)	84 (12.1)	29 (11.9)	30 (13.0)
Serious adverse event of special interest related to rhythm control therapy	22 (5.6)	4 (1.0)	31 (4.7)	8 (1.2)	12 (4.9)	5 (2.2)
Serious adverse event related to antiarrhythmic drug therapy						
Nonfatal cardiac arrest	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.4)
Drug induced bradycardia	0 (0.0)	0 (0.0)	7 (1.1)	3 (0.4)	5 (2.0)	1 (0.4)
Torsade de pointes tachycardia	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Drug toxicity of AF-related drug therapy	3 (0.8)	2 (0.5)	5 (0.8)	0 (0.0)	2 (0.8)	1 (0.4)
Atrioventricular block	1 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse event related to AF ablation						
Pericardial tamponade	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	1 (0.4)	0 (0.0)
Blood pressure related event	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Syncope	1 (0.3)	0 (0.0)	2 (0.3)	0 (0.0)	1 (0.4)	1 (0.4)
Other serious adverse event of special interest related to rhythm control therapy						
Other event	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)
Other cardiovascular event	4 (1.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Major bleeding related to AF ablation	3 (0.8)	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Hospitalization for AF	4 (1.0)	0 (0.0)	6 (0.9)	3 (0.4)	1 (0.4)	0 (0.0)
Nonmajor bleeding related to AF ablation	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)
Hospitalization for worsening of HF with decompensated HF	2 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Implantation of a pacemaker, defibrillator or other	3 (0.8)	1 (0.2)	1 (0.2)	2 (0.3)	3 (1.2)	1 (0.4)

AF, atrial fibrillation.

(1) Asymptomatic and symptomatic patients share many clinical characteristics, including similar CHA_2DS_2VASc scores with slight differences in the type of comorbidities and more first diagnosed or persistent forms of AF in asymptomatic patients.

(2) Anticoagulation and treatment of concomitant cardiovascular conditions was not different between asymptomatic and symptomatic patients.

(3) Asymptomatic patients randomized in EAST-AFNET 4 received an almost identical early rhythm control therapy compared to symptomatic patients, including AF ablation in approximately a quarter of patients still in follow-up at 2 years after randomization.

(4) The effect of rhythm control therapy on cardiovascular complications in asymptomatic patients with AF is not different to the effect in symptomatic patients and is not affected by symptom severity.

Our findings support systematic, early initiation of rhythm control therapy in all patients with AF and concomitant cardiovascular conditions independent of their AF-related symptoms (*Graphical Abstract*).

Current treatment guidelines recommend rhythm control therapy in symptomatic patients with AF only,[1,11] excluding most asymptomatic patients from this therapy.[7] These recommendations are based on earlier 'rate vs. rhythm' trials showing no effect of rhythm control therapy in cardiovascular outcomes,[12–14] including a neutral outcome in patients with recently diagnosed AF randomized to rhythm control

therapy in AFFIRM.[15] Later, the ATHENA trial randomized asymptomatic and symptomatic patients with AF to treatment with dronedarone or placebo and found a reduction in a composite of death and cardiovascular hospitalization, providing a first signal that rhythm control therapy could convey clinical benefit in patients with AF.[9] This signal was also detected in the CASTLE-AF trial comparing AF ablation to medical therapy in patients with AF and severe heart failure.[16] Both trials mainly enrolled symptomatic patients and, unlike AFFIRM, enrolled patients on continued anticoagulation. On the other hand, recent data demonstrate the safety of modern rhythm control therapy, including catheter ablation.[17–21] However, these results were obtained in symptomatic patients with a current indication for rhythm control therapy. The main findings of ATHENA,[9] CASTLE-AF,[16] and EAST-AFNET 4[8] suggest a potential clinical benefit of early rhythm control therapy, providing a sound rationale to use rhythm control therapy in asymptomatic patients with AF. The present analysis demonstrates that early and systematic initiation of rhythm control therapy in asymptomatic patients with AF enrolled in a variety of clinical settings conveys the same clinical benefit as in symptomatic patients. Further details of the therapies used to deliver the early rhythm control treatment strategy, which included AF ablation in 25% of patients randomized to early rhythm control and still in
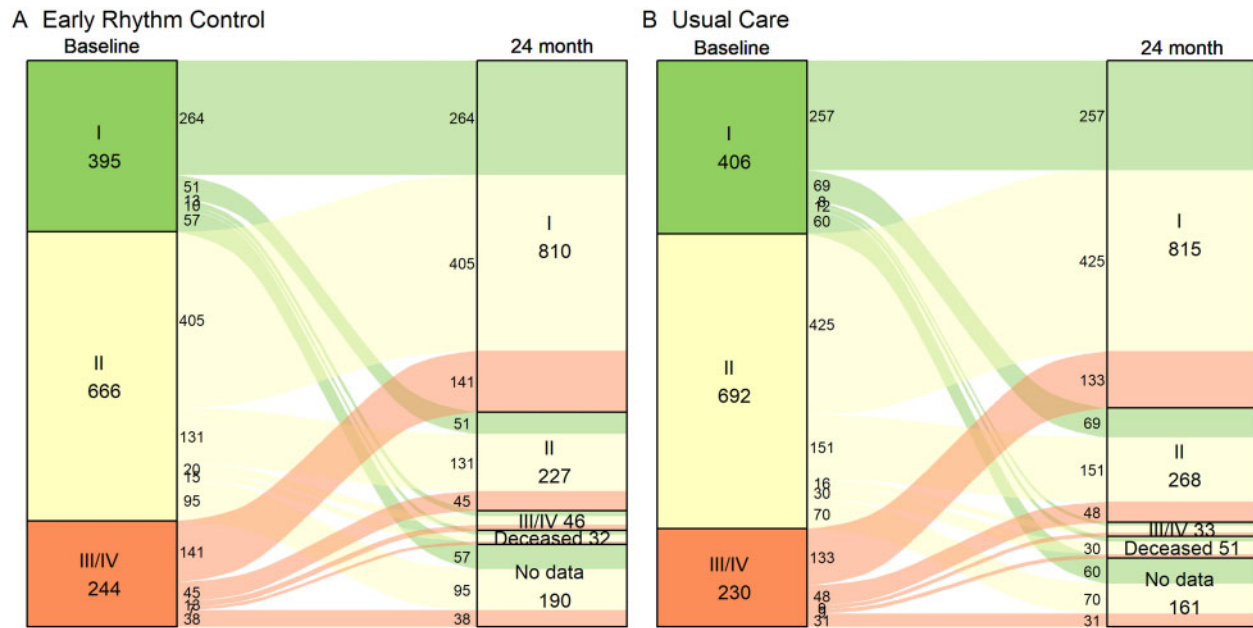
Figure 3 Change in atrial fibrillation symptoms between discharge from baseline and 24 months follow-up. There were no differences in symptom status at 24 months between randomized groups, irrespective of the presence of baseline symptoms (*P* = 0.1161). Symptoms improved without inter-group difference, illustrating the good adherence to protocol in patients randomized to usual care, which included symptom-directed rhythm control therapy to improve atrial fibrillation-related symptoms.

follow-up at two years, and antiarrhythmic drugs in 75% of patients, have been published.[22]

Clinical characteristics of asymptomatic patients with AF

Asymptomatic patients enrolled into EAST-AFNET 4 were older than symptomatic patients, had a similar CHA_2DS_2VASc score, but with slight differences in risk factor profiles, and were less frequently in paroxysmal AF (*Table 1*). This is different from the asymptomatic patients enrolled into AFFIRM and RACE who tended to be younger and had less comorbidities than symptomatic patients in those trials.[23,24] The clinical characteristics of the asymptomatic AF population in EAST-AFNET 4 replicate features of asymptomatic patients in contemporary European and American general AF registries.[4–7] These similarities suggest that the findings of this subanalysis are applicable to general patients with asymptomatic AF.

Asymptomatic patients had fewer attempts of rhythm control therapy at the time of enrolment into EAST-AFNET 4, which is in line with the current guideline recommendations restricting rhythm control therapy to the improvement of symptoms in symptomatic patients with AF.[1,11] This observation underscores the potential impact of the present analysis demonstrating a relevant reduction in the composite of cardiovascular death, stroke, or hospitalization for heart failure or acute coronary syndrome in asymptomatic patients with AF. Almost all patients enrolled into EAST-AFNET 4 had clinically diagnosed AF, which could include AF detected during routine medical visits, e.g. during vaccination. These results call for further research into the value of rhythm control therapy in patients undergoing active screening for AF.

Symptoms and quality of life in asymptomatic atrial fibrillation

The positive effect of early rhythm control on the primary outcome was not associated with improved quality of life in EAST-AFNET 4, neither in symptomatic nor in asymptomatic patients. While details of this observation remain to be analyzed, a plausible explanation is the comparator ('usual care') in EAST-AFNET 4: Patients randomized to usual care received rhythm control therapy to improve symptoms on optimal rate control.[10] About 15% of patients randomized to usual care received rhythm control therapy. This symptom-directed and delayed rhythm control therapy in patients randomized to usual care can explain the high proportion of patients with well-controlled symptoms in both randomized groups in the trial. It is possible that a higher use of AF ablation, used in 25% of asymptomatic patients with AF who were randomized to early therapy and still in follow-up at two years in this analysis, and in a similar proportion in the overall trial, could have improved quality of life even further.[19,25–27] This should be studied in future trials.

Most patients who were included in EAST-AFNET 4 without AF-related symptoms remained asymptomatic. Only 21.7% of initially asymptomatic patients became symptomatic during follow-up, with no difference between treatment groups. The results of this analysis demonstrate that systematic, early rhythm control therapy reduces cardiovascular outcomes in patients with recently diagnosed AF irrespective of AF-related symptoms. These facts invite a fundamental

rethink regarding the treatment of AF. In our view, these findings call for the inclusion of rhythm control therapy early and systematically in asymptomatic patients with AF and concomitant cardiovascular conditions.

Limitations

Although the EAST-AFNET 4 trial was a randomized, multicentre controlled trial, it was not powered for a primary analysis of asymptomatic patients. The directionality and the magnitude of the effect on the primary outcome and of its components were comparable to the effect in symptomatic patients and in the overall trial population. The 95% confidence interval of the hazard ratio for the primary outcome (0.76 [0.57, 1.03]) included 1, as could be expected due to the lower number of patients in this subgroup. Symptoms can be difficult to assess, and asymptomatic patients occasionally report improved symptoms after restoration of sinus rhythm. Furthermore, symptom assessment in this subanalysis was limited to the EHRA score, a validated[26] but general instrument capturing symptoms related to AF.

Conclusions

These results call for a shared decision process discussing the benefits of rhythm control therapy in all patients with recently diagnosed AF and concomitant cardiovascular conditions regardless of their AF-related symptoms (EAST-AFNET 4 ISRCTN number, ISRCTN04708680; ClinicalTrials.gov number, NCT01288352; EudraCT number, 2010-021258-20).

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Data availability

Data are available upon request. Please contact info@kompetenz-netz-vorhofflimmern.de.

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