JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 80, NO. 4, 2022

ORIGINAL INVESTIGATIONS

Presenting Pattern of Atrial Fibrillation and Outcomes of Early Rhythm Control Therapy

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ABSTRACT

BACKGROUND Whether atrial fibrillation (AF) pattern or timing of AF therapy modifies the effectiveness of early rhythm control (ERC) is not known.

OBJECTIVES This study sought to compare clinical characteristics and outcomes in patients presenting with different AF patterns on ERC vs usual care.

METHODS The effects of ERC were compared in first-diagnosed AF (FDAF), paroxysmal AF (paroxAF), and persistent AF (persAF) in this prespecified analysis of the EAST-AFNET 4 (Early treatment of atrial fibrillation for stroke prevention) trial. Associations between AF pattern and primary outcomes (first primary outcome: cardiovascular death, stroke, and hospitalization for heart failure and acute coronary syndrome; second primary outcome: nights spent in hospital per year) were compared over a mean follow-up of 5.1 years. Changes in health-related quality of life were assessed by the EQ-5D.

RESULTS FDAF patients (n = 1,048, enrolled 7 days after diagnosing AF) were slightly older (71 years of age, 48.0% female) than patients with paroxAF (n = 994, 70 years of age, 50.0% female) and persAF (n = 743, 70 years of age, 38.0% female). ERC reduced the primary outcome in all 3 AF patterns. Hospitalizations for acute coronary syndrome were highest in FDAF (incidence rate ratio [IRR]: 1.50; 95% CI: 0.83-2.69; *P* for interaction = 0.032) compared with paroxAF (IRR: 0.64; 95% CI: 0.32-1.25) and persAF (IRR: 0.50; 95% CI: 0.25-1.00). FDAF patients spent more nights in hospital (IRR: 1.38; 95% CI: 1.12-1.70; *P* for interaction = 0.004) than paroxAF (IRR: 0.84; 95% CI: 0.67-1.03), and persAF (IRR: 1.02; 95% CI: 0.80-1.30) patients. ERC improved health-related quality of life (EQ-5D score) in patients with paroxAF and persAF but not in patients with FDAF (*P* = 0.019).

CONCLUSIONS ERC reduces the first primary composite outcome in all AF patterns. Patients with FDAF are at high risk for hospitalization and acute coronary syndrome, particularly on ERC. (Early treatment of atrial fibrillation for stroke prevention trial; ISRCTN04708680; Early Treatment of Atrial Fibrillation for Stroke Prevention Trial [EAST]; NCT01288352; Early treatment of Atrial fibrillation for Stroke prevention Trial [EAST]; EudraCT2010-021258-20) (J Am Coll Cardiol 2022;80:283-295) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2022.04.058

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

AF = atrial fibrillation

ERC = early rhythm control

FDAF = first-diagnosed atrial fibrillation

IRR = incidence rate ratio

paroxAF = paroxysmal atrial fibrillation

persAF = persistent atrial fibrillation

Even on optimal current management, including anticoagulation and treatment of concomitant cardiovascular conditions, atrial fibrillation (AF) remains associated with severe cardiovascular complications.[1,2] Different clinical phenotypes of AF (paroxysmal AF [paroxAF] or persistent AF [persAF]) might differ with regard to clinical outcome.[2] There are few direct comparisons of different rhythm control therapies in patients with paroxAF or persAF, but rhythm control therapy can be more effective in patients with paroxAF than in those with persAF or long-standing persAF.[1] This assumption is mainly based on indirect comparisons of the effects of antiarrhythmic drugs or AF ablation between different trials.[3-6] ParoxAF has been associated with a higher risk of myocardial infarction, whereas persAF has been associated with a higher risk of stroke.[2,7-9] Typically, patients with persAF have a longer AF history than those with paroxAF, called the progressive nature of AF.[10] Therefore, it remains unclear whether this effect is due to the AF pattern itself or due to other factors influenced by time (eg, the degree of atrial cardiomyopathy).[11] To systematically compare clinical characteristics in patients presenting with different AF patterns, and to assess the effects of AF patterns on cardiovascular outcome, we compared patients with first-diagnosed AF (FDAF), paroxAF, and persAF enrolled into the EAST-AFNET 4 (Early treatment of atrial fibrillation for stroke prevention) trial.

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METHODS

The design of the EAST-AFNET 4 trial and its main results have been published.[12,13] For this prespecified analysis, patients entering the trial were grouped and analyzed in 3 groups: 1) patients with FDAF (enrolled 7 days after first clinical diagnosing of AF); 2) patients with paroxAF (duration <12 months); and 3) patients with persAF (duration <12 months).

The group of patients with FDAF encompassed 1,048 patients. ParoxAF was present in 994 patients and persAF in 743 patients. Four patients were excluded due to missing AF pattern. Patients were followed over a mean period of 5.1 years per patient. The trial was planned by AFNET (Atrial Fibrillation NETwork) and the European Heart Rhythm Association. The sponsor is AFNET (Münster, Germany). The protocol was approved by ethical review in Münster and boards for all institutions (ISRCTN04708680; NCT01288352; EudraCT2010-021258-20).[12,13]

STATISTICAL METHODS. Clinical characteristics of the patients between AF pattern groups are presented as mean ± SD or number (%). For comparison of AF pattern groups, *P* values resulting from mixed linear regression models for metric variables and mixed logistic regression models for binary categorical variables and analysis of deviance table (type II Wald chi-square tests) were calculated. Site was included as a random effect. For multinomial categorical variables, a random effect was not included.

The treatment effects were determined in each group. Cox regression models with an interaction term between treatment group and AF pattern and site as a shared frailty term were estimated for the first primary outcome and its individual components (cardiovascular death, stroke, hospitalization for worsening of heart failure, and hospitalization for acute coronary syndrome [ACS]) as well as CASTLE-AF (Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation) trial and CABANA (Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation) trial composite endpoints. The resulting treatment effects are expressed as HR with 95% CI. The second primary outcome of nights spent in hospital was modeled with a mixed negative binomial model including an interaction term for treatment group and AF pattern, the log of follow-up time as offset, and site as a random effect. The treatment effect is expressed as the incidence rate ratio (IRR) and 95% CI. Serious adverse events of special interest were analyzed with mixed logistic regression models with an interaction term for treatment group and AF pattern and a random effect for site.

Key secondary outcomes (rhythm at 2 years, left ventricular ejection fraction, quality of life, AF-related symptoms, and cognitive function) according to the EAST-AFNET 4 trial protocol were analyzed using a multiply imputed dataset after 60 imputations of missing values for a set of variables based on suggestions by White, Royston, and Wood (see statistical analysis plan in the supplement of Kirchhof

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received February 23, 2022; revised manuscript received April 14, 2022, accepted April 18, 2022.

TABLE 1 Baseline Characteristics

	Overall (N = 2,785)	AF Pattern			P Value
		First Episode (n = 1,048)	Paroxysmal (n = 994)	Persistent (n = 743)	
Age, y	70.0 ± 8.3	71.0 ± 8.1	70.0 ± 8.7	70.0 ± 8.0	0.033
Age in female subgroup, y	71.0 ± 8.1	71.0 ± 8.0	70.0 ± 8.5	72.0 ± 7.3	0.001
Age in male subgroup, y	70.0 ± 8.4	70.0 ± 8.2	69.0 ± 8.9	70.0 ± 8.3	0.34
Sex					<0.001
Female	1,293/2,785 (46.0)	507/1,048 (48.0)	501/994 (50.0)	285/743 (38.0)	
Male	1,492/2,785 (54.0)	541/1,048 (52.0)	493/994 (50.0)	458/743 (62.0)	
Patient recruitment					<0.001
Inpatient hospitalization	465/2,781 (17.0)	248/1,047 (24.0)	111/992 (11.0)	106/742 (14.0)	
Inpatient hospitalization but discharged the same day of randomization	328/2,781 (12.0)	182/1,047 (17.0)	82/992 (8.3)	64/742 (8.6)	
Outpatient visit (no overnight stay)	1,988/2,781 (71.0)	617/1,047 (59.0)	799/992 (81.0)	572/742 (77.0)	
Body mass index (calculated), kg/m^2	29.3 ± 5.4	29.3 ± 5.4	28.8 ± 5.3	29.8 ± 5.4	0.001
Sinus rhythm at baseline	1,505/2,782 (54.0)	572/1,046 (55.0)	738/993 (74.0)	195/743 (26.0)	<0.001
Days since AF diagnosis	36.0 (6.0-112.0)	7.0 (2.0-38.0)	60.0 (14.0-150.0)	77.0 (26.5-165.0)	<0.001
Absence of AF symptoms	801/2,633 (30.0)	390/1,029 (38.0)	201/901 (22.0)	210/703 (30.0)	<0.001
Previous pharmacological or electrical cardioversion	1,089/2,753 (40.0)	396/1,036 (38.0)	317/992 (32.0)	376/725 (52.0)	<0.001
LVEF, %	58.8 ± 10.0	58.7 ± 10.5	60.5 ± 8.6	56.5 ± 10.7	<0.001
LA diameter (maximal diameter), mm	43.9 ± 8.5	42.9 ± 7.8	42.0 ± 7.2	47.7 ± 9.6	<0.001
Severe coronary artery diseases (previous MI, CABG, or PCI)	478/2,785 (17.0)	172/1,048 (16.0)	163/994 (16.0)	143/743 (19.0)	0.60
Concomitant cardiovascular conditions					
Previous stroke or transient ischemic attack	328/2,785 (12.0)	115/1,048 (11.0)	129/994 (13.0)	84/743 (11.0)	0.11
At least mild cognitive impairment	1,166/2,667 (44.0)	455/999 (46.0)	378/963 (39.0)	333/705 (47.0)	0.013
Arterial hypertension	2,447/2,784 (88.0)	916/1,047 (87.0)	868/994 (87.0)	663/743 (89.0)	0.082
Systolic blood pressure, mm Hg	137 ± 19.3	137 ± 19.2	137 ± 19.4	136 ± 19.4	0.079
Diastolic blood pressure, mm Hg	81 ± 12.0	81 ± 11.8	80 ± 11.6	83 ± 12.6	<0.001
Stable HF	796/2,785 (29.0)	282/1,048 (27.0)	252/994 (25.0)	262/743 (35.0)	<0.001
CHA_2DS_2-VASc score	3.3 ± 1.3	3.3 ± 1.3	3.3 ± 1.3	3.4 ± 1.3	0.21
Chronic kidney disease stage 3 or 4	350/2,785 (13.0)	139/1,048 (13.0)	114/994 (11.0)	97/743 (13.0)	0.17
Medication at discharge					
Oral anticoagulation with DOAC or VKA	2,517/2,782 (90.0)	909/1,047 (87.0)	895/992 (90.0)	713/743 (96.0)	<0.001
Digoxin or digitoxin	131/2,782 (4.7)	39/1,047 (3.7)	20/992 (2.0)	72/743 (9.7)	<0.001
Beta-blockers	2,249/2,782 (81.0)	854/1,047 (82.0)	787/992 (79.0)	608/743 (82.0)	0.23
ACE inhibitors or angiotensin II receptor blocker	1,932/2,782 (69.0)	715/1,047 (68.0)	680/992 (69.0)	537/743 (72.0)	0.53
Mineralocorticoid receptor antagonist	182/2,782 (6.5)	51/1,047 (4.9)	60/992 (6.0)	71/743 (9.6)	<0.001
Diuretic	1,120/2,782 (40.0)	438/1,047 (42.0)	327/992 (33.0)	355/743 (48.0)	<0.001
Statin	1,196/2,782 (43.0)	409/1,047 (39.0)	448/992 (45.0)	339/743 (46.0)	0.056
Platelet inhibitor	455/2,782 (16.0)	228/1,047 (22.0)	137/992 (14.0)	90/743 (12.0)	<0.001
Planned therapy for rhythm control at baseline					0.002
AAD	1,268/2,785 (46.0)	491/1,048 (47.0)	466/994 (47.0)	311/743 (42.0)	
Ablation	114/2,785 (4.1)	30/1,048 (2.9)	37/994 (3.7)	47/743 (6.3)	
None	1,403/2,785 (50.0)	527/1,048 (50.0)	491/994 (49.0)	385/743 (52.0)	

Values are mean ± SD, n/N (%), or median (IQR). Clinical characteristics of the study population at baseline in accordance with AF pattern.

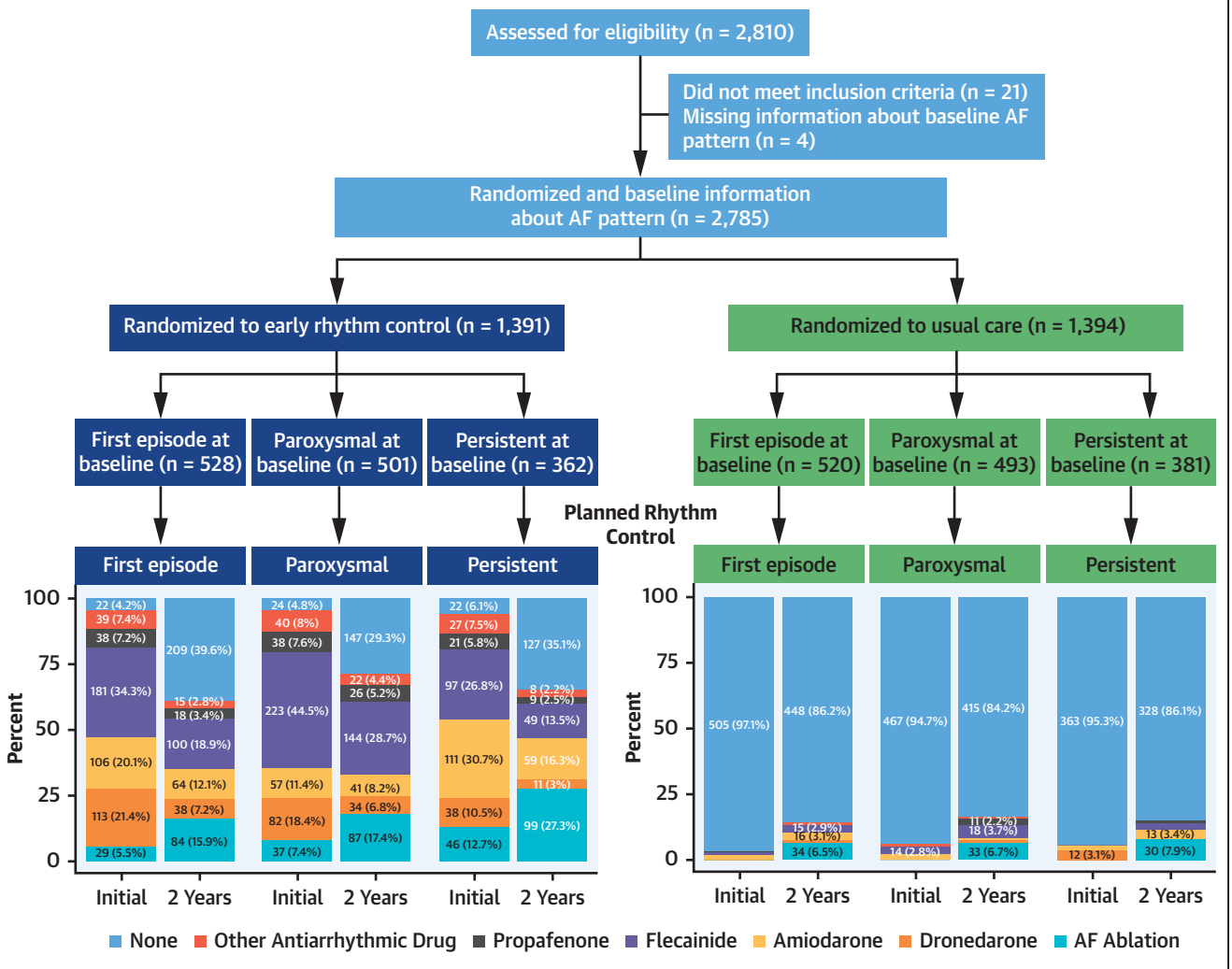
AAD = antiarrhythmic drug; ACE = angiotensin-converting enzyme; AF = atrial fibrillation; CABG = coronary artery bypass grafting; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65-74 years, sex category; DOAC = direct oral anticoagulant; HF = heart failure; LA = left atrial; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; VKA = vitamin K antagonist.

et al).[12] Mixed linear or mixed logistic models with the corresponding baseline measurement as a covariate, a treatment group by AF pattern interaction term, and site as a random effect were used where appropriate. The treatment effects are presented as the adjusted mean difference or OR with 95% CI.

Furthermore, we analyzed subgroups split for each AF pattern group by days since diagnosis of AF for the outcomes of nights spent in hospital and hospitalization for ACS with the corresponding models and parameters as mentioned previously.

For comparison with the CABANA trial and CASTLE-AF trials, we have used the outcome parameters as defined by the 2 studies.[13] For the CASTLE-AF trial, they were all-cause death or hospitalization with worsening of heart failure, and for the CABANA trial, they were all-cause death, disabling stroke, serious bleeding, or cardiac arrest.

FIGURE 1 CONSORT Diagram



Background therapy, split into patients entering the trial in sinus rhythm and in atrial fibrillation (AF), by randomized group. Initial rhythm control therapy is provided versus rate control therapy at baseline and at 2 years of follow-up.

All interaction *P* values were calculated with the likelihood ratio test, and values of $P < 0.05$ were considered statistically significant. Analyses were performed using R software, version 4.1.0 (R Foundation for Statistical Computing).

RESULTS

Patients with FDAF were slightly older (71 years of age, 48.0% female) than patients with paroxAF (70 years of age, 50.0% female) and persAF (70 years of age, 38.0% female) (Table 1). The CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65-74 years, sex category) score was comparable between AF pattern groups (median 3.3), and use of anticoagulation and treatment for concomitant cardiovascular conditions was not different (Table 1).

Overall, treatment strategies within the 2 treatment arms of the EAST-AFNET 4 trial (early rhythm control [ERC] vs usual care) did not show substantial differences between the 3 AF presentations (Figure 1 and Table 2), and ERC reduced the cardiovascular complications (first primary outcome) in all 3 AF pattern groups (*P* for interaction = 0.39) (Figure 2).

Pharmacological therapy of FDAF patients was not different compared with other AF phenotypes (Figure 1). FDAF had the lowest rates of catheter

TABLE 2 Analyses of Outcome Parameters

	First Episode		Paroxysmal		Persistent	
	Early Rhythm Control	Usual Care	Early Rhythm Control	Usual Care	Early Rhythm Control	Usual Care
First primary outcome, events per person-year (incidence per 100 person-years)	108/2,379 (4.5)	119/2,424 (4.9)	68/2,339 (2.9)	95/2,205 (4.3)	73/1,681 (4.3)	102/1,703 (6.0)
Components of first primary outcome, events per person-year (incidence per 100 person-years)						
Death from cardiovascular causes	30/2,594 (1.2)	32/2,687 (1.2)	20/2,479 (0.8)	29/2,377 (1.2)	17/1,842 (0.9)	33/1,924 (1.7)
Stroke	22/2,534 (0.9)	26/2,628 (1.0)	9/2,451 (0.4)	16/2,350 (0.7)	9/1,828 (0.5)	20/1,878 (1.1)
Hospitalization with worsening of HF	58/2,498 (2.3)	68/2,512 (2.7)	32/2,409 (1.3)	44/2,280 (1.9)	49/1,713 (2.9)	57/1,765 (3.2)
Hospitalization with ACS	27/2,514 (1.1)	19/2,625 (0.7)	14/2,436 (0.6)	21/2,319 (0.9)	12/1,812 (0.7)	25/1,872 (1.3)
Second primary outcome, nights spent in hospital per year	8.5 ± 31.0	5.1 ± 15.3	4.2 ± 15.8	5.5 ± 18.4	4.2 ± 9.9	4.5 ± 11.2
Key secondary outcomes at 2 y						
Change in LVEF, %	1.8 ± 9.6	1.7 ± 10.5	0.5 ± 9.0	-0.3 ± 8.7	2.5 ± 10.9	0.8 ± 10.1
Change in EQ-5D score	1.3 ± 18.5	1.2 ± 17.1	0.8 ± 18.1	0.8 ± 14.5	2.3 ± 15.3	0.0 ± 18.8
Change in SF-12 Mental score	0.8 ± 11.2	1.5 ± 10.8	0.4 ± 10.6	0.9 ± 9.5	1.0 ± 9.9	2.5 ± 10
Change in SF-12 Physical score	0.7 ± 8.5	0.3 ± 8.7	-0.4 ± 8.4	-0.2 ± 7.3	0.6 ± 8.6	0.1 ± 8.4
Change in MoCA score	0.1 ± 3.5	0.1 ± 3.2	0.2 ± 3.3	0.2 ± 3.5	0.0 ± 2.9	0.0 ± 2.9
Sinus rhythm	349/405 (86.2)	287/423 (67.8)	359/418 (85.9)	285/399 (71.4)	213/299 (71.2)	115/313 (36.7)
Other						
CASTLE-AF trial composite endpoint	96/2,498 (3.8)	109/2,512 (4.3)	71/2,409 (2.9)	85/2,280 (3.7)	71/1,713 (4.1)	98/1,765 (5.6)
CABANA trial composite endpoint	75/2,536 (3.0)	69/2,652 (2.6)	50/2,460 (2.0)	59/2,355 (2.5)	37/1,826 (2.0)	63/1,904 (3.3)

Values are n/N (%) or mean ± SD. The first primary endpoint and secondary primary outcomes by AF pattern. CASTLE-AF and CABANA composite endpoints in accordance to reference 25,26.

ACS = acute coronary syndrome; CABANA = Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation; CASTLE-AF = Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation; MoCA = Montreal Cognitive Assessment; SF-12 = 12-Item Short Form Survey; other abbreviations as in Table 1.

ablation at 12 months (FDAF 12.3%, paroxAF 14.2%, and persAF 24.6%) and at 24 months (FDAF 15.9%, paroxAF 17.4%, and persAF 27.3%) (Figure 1). Differences in rhythm outcomes were noted after 24 months. The majority of FDAF and paroxAF patients were in sinus rhythm during follow-up (Figure 3).

Of note, hospitalization for ACS was highest in FDAF during follow-up (IRR: 1.50; 95% CI: 0.83-2.69; *P* for interaction = 0.032) compared with paroxAF (IRR: 0.64; 95% CI: 0.32-1.25), and persAF (IRR: 0.50; 95% CI: 0.25-1.00). Patients with FDAF spent more nights in hospital (IRR: 1.38; 95% CI: 1.12-1.70; *P* for interaction = 0.004) than patients with paroxAF (IRR: 0.84; 95% CI: 0.67-1.03), and persAF (IRR: 1.02; 95% CI: 0.80-1.30). Death from cardiovascular cause, stroke, and hospitalization for worsening heart failure were not different (Table 3). Analysis of ERC vs usual care could demonstrate that FDAF patients had higher rates of second primary outcome (ie, nights spent in hospital) and hospitalization for ACS when randomized to ERC (Table 2).

Further exploratory subgroup analyses (days since AF diagnosis <10, 10-100, and >100) for each AF phenotype showed differences within phenotype groups and between AF phenotypes. Patients with FDAF with a duration <10 days spent more nights in hospital (second primary outcome) compared with the other AF patterns (Figure 4A). Hospitalizations for ACS were more common in all FDAF groups (Figure 4B). Impairment of quality of life was less affected by ERC in patients with FDAF (Table 2). The most pronounced differences between AF phenotypes were seen in the EQ-5D test.

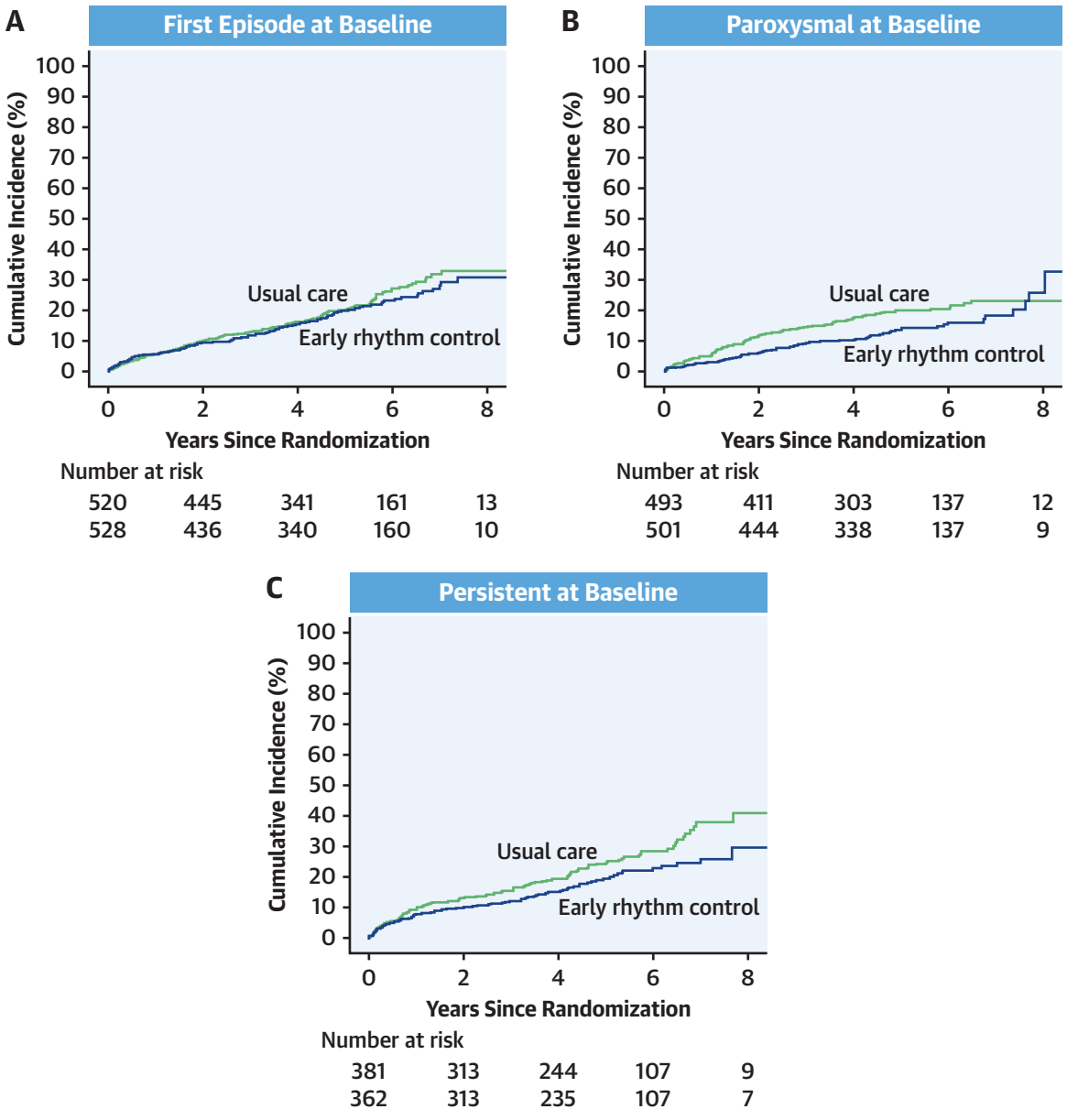
Safety outcome parameters did not show significant differences between the AF pattern groups (Table 4).

DISCUSSION

MAIN FINDINGS. ERC reduces cardiovascular death, stroke, and hospitalization for heart failure and ACS in patients with FDAF, paroxAF, or persAF, regardless of the AF pattern. Nevertheless, the AF phenotype has an impact on clinical outcome: Patients with FDAF are at a higher risk of hospitalization and ACS during follow-up, in particular patients treated with ERC. Furthermore, quality of life appears to improve less in FDAF patients compared with the 2 other AF patterns.

Effect of ERC. Rhythm control therapy, and especially AF ablation, is perceived to be more effective in patients with paroxAF than in patients with persAF.[1,5,6,14,15] This analysis demonstrates the effectiveness of ERC in patients with FDAF, paroxAF, and persAF. It is conceivable that the AF pattern in other studies enrolling patients with a longer AF

FIGURE 2 Impact of Atrial Fibrillation Pattern on Primary Outcome



(A) First-diagnosed atrial fibrillation (AF) group; **(B)** paroxysmal AF goup; **(C)** persistent AF group. First primary outcome in the 3 atrial fibrillation pattern groups by treatment group (*P* for interaction = 0.39).

duration is a proxy for atrial damage[11] or AF duration.[2] Whether rhythm control therapy is effective in patients with chronic AF patterns and longer AF duration cannot be deduced from this analysis.

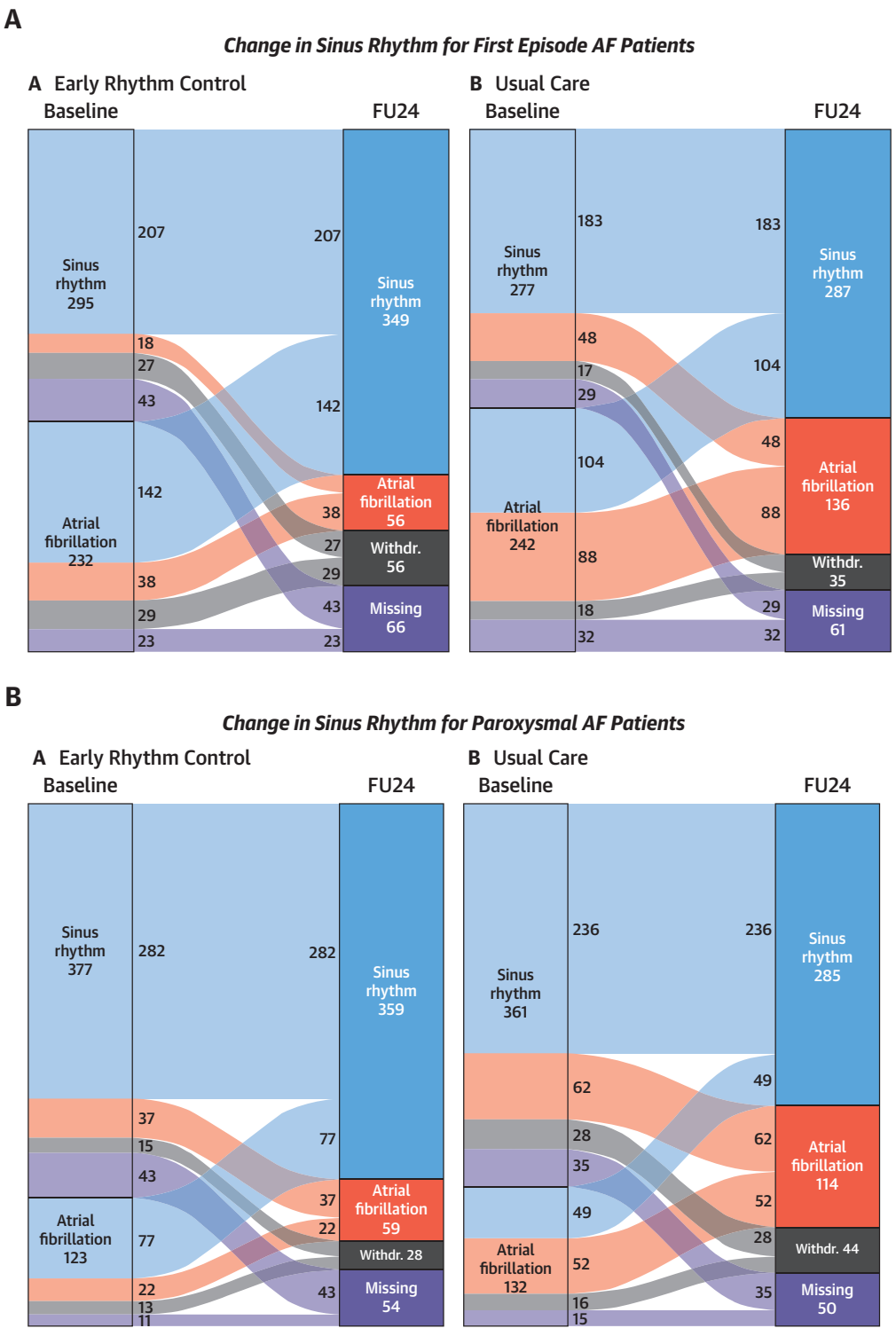
Higher risk of hospitalization and reduced improvement of quality of life in FDAF. Epidemiological studies and registries showed that patients with AF have a higher mortality rate and increased risk for heart failure and ACS.[2,16] However, the impact of the specific AF pattern in relation to treatment strategies on events requiring hospitalization has not been explored in a randomized trial so far. Thus, the EAST-AFNET 4 trial provides the first evidence in a large group of AF patients with a long follow-up (5 years) that there are subtle differences in particular for patients with FDAF. This is relevant because the first documented AF episode can be easily determined. Patients with

FDAF had slightly different baseline characteristics, particularly in comparison with patients with persAF: AF duration before first diagnosis was very short (median 7.0 days), and about 50% of included FDAF patients were women. Blood pressure values were lower, and stable heart failure was less common in FDAF compared with persAF. Patients with persAF (in particular, >100 days for first AF diagnosis), more often showed impaired left ventricular ejection fraction and reduced quality of life during follow-up. In contrast, rates of cardiovascular death and stroke were lower in persAF. Overall, the increased hospitalization rates and the higher incidence of ACS in FDAF patients appear to be relevant factors, which help to explain reduced quality-of-life measures in subgroup of AF patients.

Overlap of outcome and risk between AF patterns. This analysis clearly shows that AF pattern phenotypes overlap substantially with regard to outcome: cardiovascular and noncardiovascular events occurred frequently in all 3 AF pattern groups. This might be explained by difficulties to identify a specific AF phenotype in an AF patient. There is large variability in AF occurrence within patients, and patients may move from paroxAF to persAF and back; therefore, one phenotype might not be representative for a specific patient. This intraindividual variability of AF phenotypes must be considered if AF phenotypes are used to assess outcome. Although the duration of AF prior to diagnosis will vary in patients with FDAF, especially when they are asymptomatic, this group can be easily defined in clinical practice. Our results show that FDAF is associated with a higher risk of some AF-related complications during a 5-year follow-up, highlighting the need for intensified risk reduction in patients with FDAF. In contrast to FDAF, previous studies of the EAST-AFNET 4 trial have shown that other AF subgroups like asymptomatic AF patients or AF patients with heart failure show a clear benefit from ERC.[17,18]

Epidemiological data suggested prior to the start of EAST-AFNET 4 trial that mortality and morbidity may be highest in the first year after diagnosing AF.[19] This might relate to the new detection of both AF itself (FDAF) and possibly also to associated diseases, which implies more often unstable and less well-managed patients when compared with already diagnosed patients with chronic paroxAF and persAF. Pathophysiologically, acute episodes of AF might be triggered by severe or acute disease, leading to a first diagnosis of AF. Our data support the higher risk associated with FDAF. In addition, the occurrence of the first AF episode might characterize different sets of patients as a biomarker of transient systemic, biological, and atrial electrical instability during pathological conditions such as acute heart failure, hypertensive crisis, hyperthyroidism, electrolyte disturbances, sepsis etc.[10,11] Thus, FDAF might characterize different AF subgroups compared with chronic AF phenotypes. Of note, we found that >70.0% of FDAF patients were in sinus rhythm at 24 months regardless of the used treatment strategy. In contrast, the higher rate of sinus rhythm in FDAF during ERC was related to a greater number of nights spent in hospital and hospitalization for ACS, whereas the rate of stroke or heart failure was not affected. Furthermore, quality of life did not improve during follow-up in FDAF. Thus, recurrence of AF appears to be of minor importance to explain the observed differences in hospitalization and quality of life in this subgroup. Our data support the notion that FDAF might be seen as an additional clinical marker identifying high-risk patients. It might be speculated that acute episodes of AF might in addition have contributed to outcomes in the FDAF group. Acute AF has been shown to induce substantial hemodynamic changes in organ perfusion.[20,21] Owing to AF-induced oxidative stress at the cellular level, microcirculatory flow abnormalities can occur in particular in the ventricles of the heart. Thereby, type I myocardial infarctions may occur due to limited flow across pre-existing stenoses in epicardial coronary arteries, or AF might induce type II myocardial infarctions.[9,16,22,23] Some of the experimentally observed changes may help to explain the present findings in FDAF patients. In patients with longer episodes of AF, oxidative stress is counterbalanced by several adaptive molecular processes; therefore, acute ischemic cardiac events might occur less often in persAF compared with FDAF. Latest results of the ENSURE AF (Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation) and ENTRUST AF PCI (Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation) trials could show that patients with brief AF episodes have higher rates of acute coronary events compared with patients with non-paroxAF.[9,22] In addition, the SCAF (Stockholm Cohort-Study of atrial fibrillation) study showed that patients with paroxAF are at risk of myocardial infarction.[16] However, in most studies, different patterns of AF were not assessed.[24] In particular, patients with FDAF were not classified as a separate pattern of AF in most studies.[2,16,23,24] Thus, it might be speculated that FDAF was counted as paroxAF in many registries; therefore, previous studies might

FIGURE 3 Documented Cardiac Rhythm During Follow-Up



Sankey plots of cardiac rhythm at baseline and during follow-up in the 3 different atrial fibrillation (AF) patterns with regard to the used treatment strategy: **(A)** first-diagnosed AF, **(B)** paroxysmal AF, and **(C)** persistent AF. Withdr. = withdrawn; FU24 = 24-month follow-up.

Continued on the next page

FIGURE 3 Continued

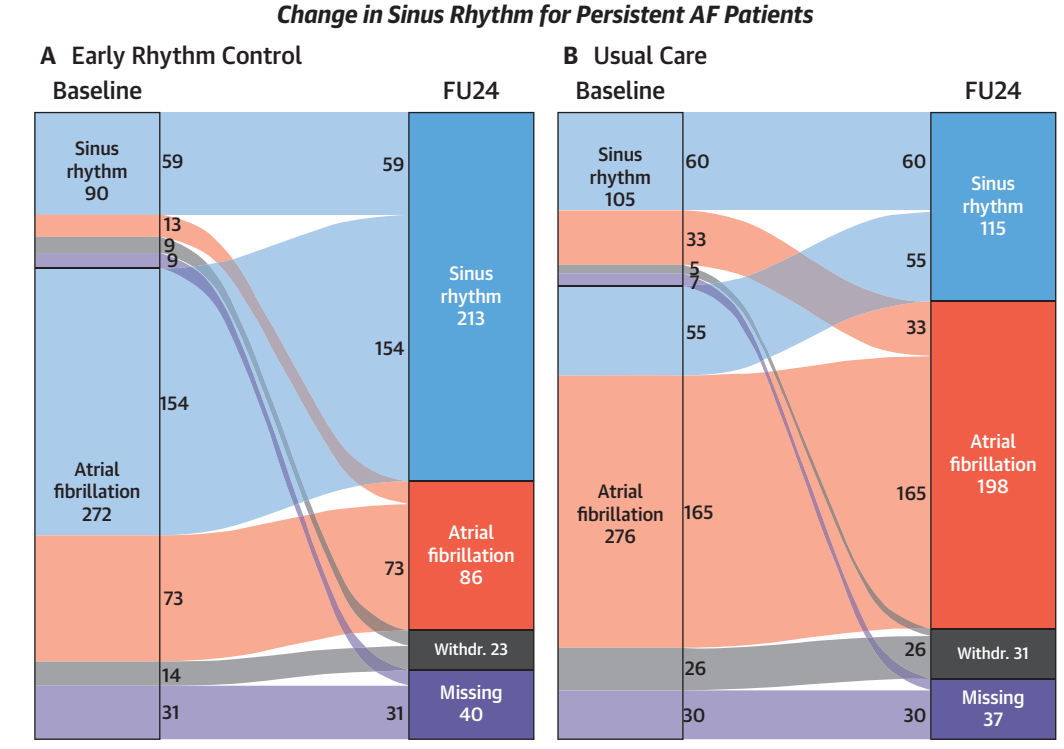


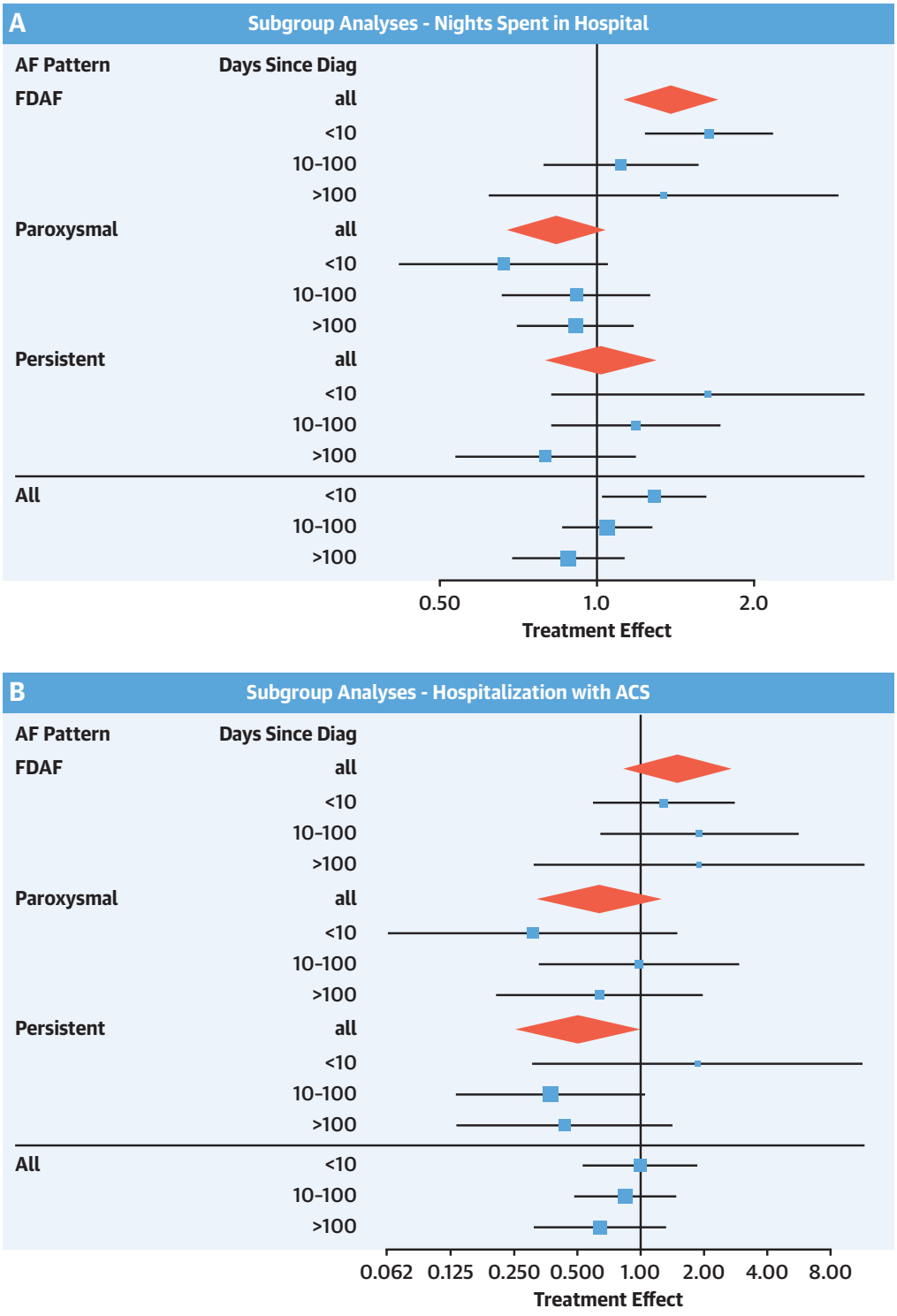
TABLE 3 Treatment Effects in AF Patterns

	Treatment Effect			*P* Value for Interaction
	First Episode	Paroxysmal	Persistent	
First primary outcome	0.91 (0.70 to 1.18)	0.67 (0.49 to 0.91)	0.76 (0.56 to 1.03)	0.391
Death from cardiovascular causes	0.96 (0.58 to 1.57)	0.65 (0.37 to 1.15)	0.56 (0.31 to 1.00)	0.325
Stroke	0.88 (0.50 to 1.56)	0.54 (0.24 to 1.22)	0.47 (0.21 to 1.02)	0.342
Hospitalization with worsening of heart failure	0.84 (0.59 to 1.19)	0.68 (0.43 to 1.07)	0.94 (0.64 to 1.38)	0.364
Hospitalization with ACS	1.50 (0.83 to 2.69)	0.64 (0.32 to 1.25)	0.50 (0.25 to 1.00)	0.032
Secondary primary outcome, nights spent in hospital per year	1.38 (1.12 to 1.70)	0.84 (0.67 to 1.03)	1.02 (0.80 to 1.30)	0.004
Change in LVEF	0.22 (−0.88 to 1.32)	−0.08 (−1.27 to 1.1)	0.68 (−0.67 to 2.03)	0.706
Change in EQ-5D score	−2.16 (−5.15 to 0.84)	2.49 (−0.53 to 5.51)	3.96 (0.58 to 7.33)	0.019
Change in SF-12 Mental score	−1.52 (−2.88 to −0.17)	−0.92 (−2.27 to 0.44)	−1.02 (−2.61 to 0.57)	0.801
Change in SF-12 Physical score	0.20 (−0.95 to 1.36)	0.08 (−1.15 to 1.31)	0.94 (−0.39 to 2.27)	0.613
Change in MoCA score	−0.25 (−0.67 to 0.17)	0.05 (−0.39 to 0.49)	−0.21 (−0.69 to 0.28)	0.583
Sinus rhythm	2.77 (1.94 to 3.97)	2.46 (1.73 to 3.49)	4.79 (3.38 to 6.80)	0.019
CASTLE-AF trial composite endpoint: all-cause death or hospitalization with worsening of heart failure	0.87 (0.66 to 1.15)	0.77 (0.56 to 1.06)	0.79 (0.58 to 1.07)	0.891
CABANA trial composite endpoint: all-cause death, disabling stroke, serious bleeding, or cardiac arrest	1.14 (0.82 to 1.59)	0.79 (0.54 to 1.16)	0.63 (0.42 to 0.94)	0.081

Values are incidence rate ratio (95% CI). Treatment effects of early rhythm control versus usual care in the 3 different AF pattern groups. CASTLE-AF trial and CABANA trial composite endpoints in accordance to Marrouche et al[25] and Packer et al.[26]

Abbreviations as in Tables 1 and 2.

FIGURE 4 Subgroup Analysis for AF Patterns



Group split by days since diagnosis (Diag) of atrial fibrillation (AF) in patients with first-diagnosed AF (FDAF), paroxysmal AF, and persistent AF for **(A)** nights spent in hospital and **(B)** hospitalization with an acute coronary syndrome (ACS).

TABLE 4 Safety Outcomes by Baseline AF Pattern and Randomized Group

	First Episode		Paroxysmal		Persistent		
	Early Rhythm Control (n = 528)	Usual Care (n = 520)	Early Rhythm Control n = 501)	Usual Care (n = 493)	Early Rhythm Control (n = 362)	Usual Care (n = 381)	*P* Value for Interaction
Primary composite safety outcome	103 (19.5)	80 (15.4)	70 (14.0)	65 (13.2)	58 (16.0)	78 (20.5)	0.086
Stroke	22 (4.2)	26 (5.0)	9 (1.8)	16 (3.2)	9 (2.5)	20 (5.2)	0.45
Death	60 (11.4)	55 (10.6)	45 (9.0)	55 (11.2)	33 (9.1)	54 (14.2)	0.203
Serious adverse event of special interest related to RC therapy	29 (5.5)	5 (1.0)	21 (4.2)	5 (1.0)	18 (5.0)	9 (2.4)	0.257
Serious adverse event related to AAD therapy							
Nonfatal cardiac arrest	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.3)	0.258
Drug induced bradycardia	7 (1.3)	1 (0.2)	4 (0.8)	1 (0.2)	3 (0.8)	3 (0.8)	0.305
Torsades de pointes tachycardia	0 (0.0)	0 0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1
Drug toxicity of AF-related drug therapy	6 (1.1)	1 (0.2)	2 (0.4)	2 (0.4)	2 (0.6)	0 (0.0)	0.243
Atrioventricular block	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1
Serious adverse event related to AF ablation							
Pericardial tamponade	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	1
Blood pressure–related event	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1
Syncope	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)	1 (0.3)	0.775
Serious adverse event of special interest related to RC therapy							
Other event	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	2 (0.5)	0.531
Other cardiovascular event	3 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.6)	0 (0.0)	0.045
Major bleeding related to AF ablation	4 (0.8)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1
Hospitalization for AF	3 (0.6)	2 (0.4)	4 (0.8)	0 (0.0)	4 (1.1)	1 (0.3)	0.235
Nonmajor bleeding related to AF ablation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.5)	1
Hospitalization for worsening of HF with decompensated HF	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	1
Implantation of a pacemaker, ICD, or other	2 (0.4)	1 (0.2)	5 (1.0)	1 (0.2)	1 (0.3)	2 (0.5)	0.365

Values are n (%).
ICD = implantable cardioverter-defibrillator; RC = rhythm control; other abbreviations as in Table 1.

have seen a higher risk for ventricular ischemia in patients with short AF episodes (FDAF/paroxAF) vs persAF. Furthermore, it remains unclear if a potential interaction between rhythm control therapy per se and ventricular ischemia has contributed to the increased adverse outcome in FDAF patients.

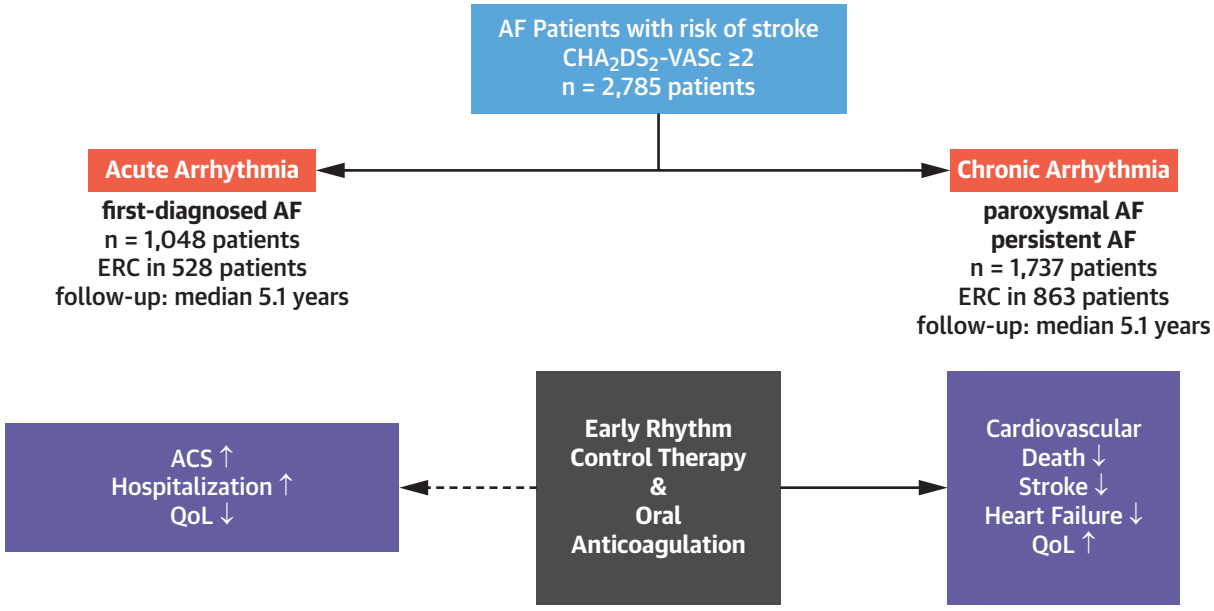
The occurrence of stroke is reduced by adequate oral anticoagulation in AF patients with established stroke risk factors. In our trial, more than 90.0% of all patients were anticoagulated. However, ERC reduced the rate of stroke, which shows that restoration of sinus rhythm per se prevents cerebral ischemia. Previous studies suggest that the burden of AF or the AF phenotype predict the risk of stroke.[2,16,23] This cannot be supported by the present analyses, as we could not clearly detect differences in the stroke rates between AF phenotypes. Nevertheless, the overall size of various AF subgroups is too small to draw definitive conclusions with regard to the 2 different treatment strategies used in this trial. However, the present analyses are also important for comparison with other trials in this field.[25,26]

STUDY LIMITATIONS. The EAST-AFNET 4 trial was a randomized, multicenter controlled trial. It was not sufficiently powered for this subgroup analysis. However, this analysis enabled a direct comparison of the effect of ERC therapy based on rhythm at baseline and AF pattern. For the first time, this analysis was not or was only minimally affected by AF duration, as this was limited to 1 year in all patients entering the trial. Furthermore, the EAST-AFNET 4 trial did not use electrocardiographic monitoring throughout the trial. Thus, this analysis was limited to AF pattern and could not include AF burden. Patients were not entirely treatment-naïve at the time of randomization. While randomization eliminated biases between treatment groups, selection biases between AF patterns cannot fully be excluded. Patients with FDAF were classified in accordance of the first clinical diagnosis of AF within the last 7 days. Nevertheless, we cannot rule out that these patients had asymptomatic episodes of AF before randomization into the EAST-AFNET 4 trial.

CONCLUSIONS

ERC reduces cardiovascular complications (cardiovascular death, stroke, hospitalization for heart

CENTRAL ILLUSTRATION **Impact of Early Rhythm Control Therapy on AF Patterns**



Goette A, et al. J Am Coll Cardiol. 2022;80(4):283–295.

Early rhythm control (ERC) therapy improved the composite outcome mainly in patients with chronic paroxysmal and persistent atrial fibrillation (AF) (cardiovascular death, stroke, hospitalization for heart failure, and quality of life [QoL]). In contrast to the composite outcome in the overall EAST-AFNET 4 (Early treatment of atrial fibrillation for stroke prevention) trial population, occurrence of acute coronary syndrome (ACS) and nights spent in hospital were increased and QoL was reduced in patients with first-diagnosed AF (eg, acute arrhythmia), particularly on ERC. CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65-74 years, sex category

failure) across all AF patterns. Patients presenting with FDAF do not clearly benefit from ERC with regard to hospitalization and ACS during follow-up (Central Illustration). Thus, FDAF might serve as a simple biomarker that helps to identify patients at higher risk for ACS and other medical conditions.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Goette was partially supported by the EU Horizon 2020 MAESTRIA Consortium (grant number 965286). Dr Kirchhof was partially supported by the EU BigData@Heart (grant agreement EU IMI 116074), AFFECT-AF (grant agreement 847770), and MAESTRIA (grant agreement 965286); the British Heart Foundation (PG/17/30/32961; PG/20/22/35093; AA/18/2/34218), the German Centre for Cardiovascular Research supported by the German Ministry of Education and Research, and the Leducq Foundation. The EAST-AFNET 4 trial was supported by AFNET, the European Heart Rhythm Association, the German Centre for Cardiovascular Research, the German Heart Foundation, Sanofi, and Abbott. Dr Goette has received speaker fees from Abbott, AstraZeneca, Bayer Health Care, Berlin Chemie, Biotronik, Boehringer Ingelheim, BMS/Pfizer, Boston Scientific, Daiichi-Sankyo, Medtronic, Omeicos, Sanofi, and Viofor. Dr Camm has served as an advisor for Bayer, Daiichi-Sankyo, Pfizer/BMS, Medtronic, Boston Scientific, Abbott, Menarini, and Sanofi. Dr Kuck has served as a consultant for CardioValve; and has received grant support from Medtronic and Biosense Webster. Dr Wegscheider has served as a lecturer and statistical consultant for Biotronik, Boston Scientific, and Novartis; and has received grant support from Biotronik and Resmed. Dr Kirchhof has received research support for basic, translational, and clinical research projects from the European Union, British Heart Foundation, Leducq Foundation, Medical Research Council (United Kingdom), and German Centre for Cardiovascular Research and from several drug and device companies active in atrial fibrillation; has received honoraria from several such companies in the past, but not in the last 3 years; and has been listed as inventor on 2 patents held by University of Birmingham (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: ERC reduces cardiovascular complications in patients with FDAF, paroxAF, and persAF, but patients with FDAF managed with ERC strategies face higher risks of hospitalization and ACS than those with paroxAF or persAF.

TRANSLATIONAL OUTLOOK: More research is needed to understand how the circumstances under which AF is first identified is related to subsequent ACS, particularly when ERC therapy is employed.

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KEY WORDS acute coronary syndrome, atrial fibrillation, heart failure, hospitalization, outcome, stroke, therapy