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Early Rhythm Control in Patients With Atrial Fibrillation and High Comorbidity Burden

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BACKGROUND: The randomized EAST-AFNET4 (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial–Atrial Fibrillation Network) demonstrated that early rhythm control (ERC) reduces adverse cardiovascular outcomes in patients with recently diagnosed atrial fibrillation and stroke risk factors. The effectiveness and safety of ERC in patients with multiple cardiovascular comorbidities is not known.

METHODS: These prespecified subanalyses of EAST-AFNET4 compared the effectiveness and safety of ERC with usual care (UC) stratified into patients with higher (CHA_2DS_2-VASc score ≥4) and lower comorbidity burden. Sensitivity analyses ignored sex (CHA_2DS_2-VA score).

RESULTS: EAST-AFNET4 randomized 1093 patients with CHA_2DS_2-VASc score ≥4 (74.8±6.8 years, 61% female) and 1696 with CHA_2DS_2-VASc score <4 (67.4±8.0 years, 37% female). ERC reduced the composite primary efficacy outcome of cardiovascular death, stroke, or hospitalization for worsening of heart failure or for acute coronary syndrome in patients with CHA_2DS_2-VASc score ≥4 (ERC, 127/549 patients with events; UC, 183/544 patients with events; hazard ratio [HR], 0.64 [0.51–0.81]; $P<0.001$) but not in patients with CHA_2DS_2-VASc score <4 (ERC, 122/846 patients with events; UC, 133/850 patients with events; HR, 0.93 [0.73–1.19]; $P=0.56$, $P_{interaction}=0.037$). The primary safety outcome (death, stroke, or serious adverse events of rhythm control therapy) was not different between study groups in patients with CHA_2DS_2-VASc score ≥4 (ERC, 112/549 patients with events; UC, 132/544 patients with events; HR, 0.84 [0.65, 1.08]; $P=0.175$), but occurred more often in patients with CHA_2DS_2-VASc scores <4 randomized to ERC (ERC, 119/846 patients with events; UC, 91/850 patients with events; HR, 1.39 [1.05–1.82]; $P=0.019$, $P_{interaction}=0.008$). Life-threatening events or death were not different between groups (CHA_2DS_2-VASc score ≥4, ERC, 84/549 patients with event, UC, 96/544 patients with event; CHA_2DS_2-VASc scores <4, ERC, 75/846 patients with event, UC, 73/850 patients with event). When female sex was ignored for the creation of higher and lower risk groups (CHA_2DS_2-VA score), the $P_{interaction}$ was not significant for the primary efficacy outcome ($P=0.25$), but remained significant ($P=0.044$) for the primary safety outcome.

CONCLUSIONS: Patients with recently diagnosed atrial fibrillation and CHA_2DS_2-VASc score ≥4 should be considered for ERC to reduce cardiovascular outcomes, whereas those with fewer comorbidities may have less favorable outcomes with ERC.

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Clinical Perspective

What Is New?

- These prespecified subanalyses of EAST-AFNET4 (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial–Atrial Fibrillation Network) found that early rhythm control therapy reduces a composite of cardiovascular death, stroke, or hospitalization for heart failure or acute coronary syndrome in patients with recently diagnosed atrial fibrillation and a high comorbidity burden (CHA_2DS_2-VASc score ≥4).
- In patients with fewer comorbidities, early rhythm control as tested in EAST-AFNET4 was not superior to usual care but increased therapy-related bradycardia, atrial fibrillation–related hospitalizations, and drug toxicity without differences in life-threatening events between randomized groups independent of comorbidity burden.
- When sex was ignored to estimate comorbidity burden (CHA_2DS_2-VA score), the results showed a similar direction in patients with CHA_2DS_2-VA scores ≥4, but the interaction between early rhythm control and comorbidity burden was no longer significant.

What Are the Clinical Implications?

- Patients with recently diagnosed atrial fibrillation and CHA_2DS_2-VASc scores ≥4 should be preferentially treated with early rhythm control.
- Among patients with fewer comorbidities, the risk/benefit of early rhythm control may not be favorable.
- Avoiding bradycardia and drug toxicity could improve the safety of early rhythm control in the future.
- Dedicated clinical trials are needed to test these hypothesis-generating findings.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
ATHENA	A Trial With Dronedarone to Prevent Hospitalization or Death in Patients With Atrial Fibrillation
CABANA	Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation
EAST-AFNET4	Early Treatment of Atrial Fibrillation for Stroke Prevention Trial–Atrial Fibrillation Network
ERC	early rhythm control
HF	heart failure
HR	hazard ratio
UC	usual care

Rhythm control therapy, consisting of antiarrhythmic drug therapy or atrial fibrillation (AF) ablation, can prevent some but not all recurrences of AF and is primarily recommended to improve quality of life in patients with symptomatic AF.[1,2] Concerns over its safety are a main reason to withhold rhythm control therapy in patients with AF, especially in those with cardiovascular comorbidities.[1,2] EAST-AFNET4 (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial–Atrial Fibrillation Network) demonstrated that early, systematic initiation of rhythm control therapy can contribute to reduction of cardiovascular complications in patients with recently diagnosed AF and comorbidities.[3] This finding was consistent in patients with heart failure (HF)[4] and regardless of symptoms[5] and corroborates earlier observations in the randomized, placebo-controlled ATHENA (A Trial With Dronedarone to Prevent Hospitalization or Death in Patients With Atrial Fibrillation).[6,7] Several health care database analyses confirm the overall safety of modern rhythm control therapy.[8]

However, data on the effectiveness[9,10] and safety[11–14] of rhythm control therapy in patients with higher comorbidity burden are on the basis of small cohorts and yield conflicting results. In view of the large number of patients with AF and several cardiovascular comorbidities, and of their elevated risk of AF-related complications,[15–17] specific information on the effectiveness and safety of early rhythm control (ERC) therapy in patients with multiple comorbidities is needed.

To estimate the effectiveness and safety of ERC therapy in older patients with cardiovascular comorbidities, these prespecified subanalyses of the randomized EAST-AFNET4 assessed whether presence of cardiovascular comorbidities as summarized by a high CHA_2DS_2-VASc score modifies the treatment effect of ERC therapy in the EAST-AFNET4 data set.

METHODS

In brief, EAST-AFNET4 was an international, investigator-initiated, parallel-group, randomized, open, blinded outcome assessment trial. The trial randomized 2789 patients with AF diagnosed within 12 months and at least 2 CHA_2DS_2-VASc risk factors to either ERC therapy (n=1395) or usual care (UC; n=1394).[3] ERC consisted of antiarrhythmic drug therapy, catheter ablation, or cardioversion in all patients after randomization. In patients assigned to UC, rate control was the initial strategy and rhythm control was reserved for patients who remained symptomatic on optimal rate control therapy.[3] Anticoagulation therapy and treatment of concomitant conditions was not different between randomized groups.[18]

The first primary outcome was a composite of death from cardiovascular causes, stroke, or hospitalization with worsening of HF or acute coronary syndrome. The second primary outcome was the number of nights spent in the hospital. The primary safety outcome was a composite of death, stroke, or serious adverse events related to rhythm control therapy.

For safety analyses, the definitions provided in the study protocol as part of the supplemental material to the main article were used (see protocol chapter 8).[3] In brief, proarrhythmia was defined as any arrhythmic event or an event with a potential arrhythmic background that was judged as causally related to the therapeutic intervention (e.g., drug-induced proarrhythmia [torsade de pointes, ventricular tachycardia, ventricular fibrillation], drug-induced bradycardia, atrioventricular block, ablation-induced or drug-induced atrial arrhythmias [left atrial flutter], or syncope).[3] Any other event judged as causally related to the therapies applied within the trial (e.g., bleeding events caused by AF ablation or antithrombotic therapy, complications of ablation procedures [pulmonary vein stenosis, pericardial tamponade, atrio-esophageal fistula], drug toxicity of AF-related drug therapy, or others) was also counted.[3] Adverse events were classified as serious if they resulted in death, were life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability, resulted in incapacity, resulted in a congenital anomaly or birth defect, or were judged medically important.[3]

For assessment of arrhythmia recurrence, ECGs were collected in all patients at 1 and 2 years. Patients assigned to ERC received patient-operated ECGs enabling 30-second single-lead ECG recordings (Vitaphone) and were asked to transmit 3 ECGs per week plus an ECG when symptomatic.[18] Secondary outcomes were defined as given in the study protocol (supplemental material to the main article; see protocol).[3]

All analyses reported here were performed in the final, locked data set assigning patients to therapy group on the basis of randomization (intention-to-treat population). Data will be made available on reasonable request (contact: info@kompetenznetz-vorhofflimmern.de).

The protocol was approved by the ethics review boards of all institutions involved. All patients participating in the trial provided written informed consent.

Statistics

These prespecified subanalyses categorized all patients randomized in EAST-AFNET4 on the basis of their comorbidities and age into higher CHA_2DS_2-VASc score (≥4) or lower CHA_2DS_2-VASc score (<4). Because age is a key predictor of cardiovascular complications in patients with AF and in the general population interacting with outcomes in subanalyses of the CABANA trial (Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation),[19] additional post hoc analyses also compared outcomes in the following age categories: <65 years, 65 to 74 years, and ≥75 years.

Patients' baseline characteristics were summarized with descriptive statistical methods. Categorical data are summarized as absolute and relative frequencies and continuous variables described by mean and SD or median (first and third quantile).

The primary efficacy and safety outcomes of the overall population of EAST-AFNET4 were analyzed in separately patients with higher (≥4) and lower (<4) CHA_2DS_2-VASc scores.

For calculation of the first primary outcome, a Cox proportional hazards model with a frailty term for the cluster center was used. The same model was used for the analyses of further time-to-event outcomes such as time to cardiovascular death, first stroke, first hospitalization for worsening HF, first hospitalization for acute coronary syndrome, all-cause death, or the primary safety outcome. The treatment effects are expressed as cause-specific hazard ratios (HRs) and corresponding 95% CIs.

To account for the competing event all-cause death within the primary outcome analyses, the Aalen-Johansen estimator was used to estimate survival curves.

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 by using total sum of nights and a negative binomial mixed model. The treatment effect is shown as incidence rate ratio and 95% CI.

Baseline-adjusted mixed linear models were implemented for continuous secondary outcomes after applying a multivariable imputation with chained equations algorithm with 60 imputations of missing values for a prespecified set of variables on the basis of suggestions by White, Royston, and Wood (see statistical analyses plan in the supplement of reference [3]) and expressed as the adjusted mean difference and 95% CI.

As sensitivity analyses, we repeated the analyses without the sex component of the original CHA_2DS_2-VASc score (i.e., we stratified all patients into CHA_2DS_2-VA <4 or ≥4). Sinus rhythm and symptoms at 24 months were analyzed by using mixed logistic models on the same multiply imputed dataset and shown as the odds ratio and 95% CI. The main analyses and these sensitivity analyses were repeated with and without imputations for secondary outcomes. Definitions of missing values and multiple imputations were used as described in the supplement of the main article.[3] Statistical software R version 4.1.0 was used for all analyses.

RESULTS

Baseline Characteristics

Of the 2789 patients randomized in EAST-AFNET4, 1093 had a CHA_2DS_2-VASc score ≥4 and 1696 had a CHA_2DS_2-VASc score <4. There were no differences between randomized groups in either of the 2 CHA_2DS_2-VASc score strata (Table 1). As expected, patients with high CHA_2DS_2-VASc ≥4 were older, were more often women, and had a higher prevalence of the other components of the score (HF, diabetes, previous stroke, and vascular disease; see Table 1 and Table S1). The use of therapies treating the comorbidities forming the score was higher in patients in the CHA_2DS_2-VASc ≥4 stratum, as expected (Table 1 and Table S1). Oral anticoagulation use was 3% lower in patients with CHA_2DS_2-VASc score <4 (n=1510/1691 patients [89%]) than in those with a CHA_2DS_2-VASc score ≥4 (n=1007/1091 patients [92%]; P=0.005; Table 1 and Table S1). There was no difference in the use and type of rate-controlling agents between the CHA_2DS_2-VASc score strata. Across both strata, therapy of concomitant conditions was not different between randomized groups (Table 1 and Table S1).

Table 1. Clinical Characteristics of the Population by CHA_2DS_2-VASc Score

Characteristics	Lower comorbidity burden (CHA_2DS_2-VASc score <4)		Higher comorbidity burden (CHA_2DS_2-VASc score ≥4)	
	ERC (n = 846)	UC (n = 850)	ERC (n = 549)	UC (n = 544)
Age, y	67 (8.1)	67 (7.8)	75 (6.9)	75 (6.6)
Female sex	308/846 (36)	320/850 (38)	337/549 (61)	328/544 (60)
Body mass index (calculated), kg/m²	29.2 (5.5)	29.5 (5.3)	29.2 (5.3)	29.0 (5.4)
AF type				
First episode	320/844 (38)	321/850 (38)	208/547 (38)	199/544 (37)
Paroxysmal	304/844 (36)	299/850 (35)	197/547 (36)	194/544 (36)
Persistent or longstanding persistent	220/844 (26)	230/850 (27)	142/547 (26)	151/544 (28)
Sinus rhythm at baseline	477/842 (57)	477/850 (56)	285/547 (52)	266/543 (49)
Days since AF diagnosis	39.0 (7.0, 118.0)	41.0 (6.0, 107.0)	29.5 (5.0, 102.2)	28.0 (5.0, 112.2)
Absence of AF symptoms	236/790 (30)	242/812 (30)	159/515 (31)	164/516 (32)
Previous pharmacologic or electrical cardioversion	348/828 (42)	337/847 (40)	198/536 (37)	206/542 (38)
Concomitant cardiovascular conditions				
Previous AF ablation	0/846 (0)	0/850 (0)	0/549 (0)	3/544 (0.6)
Previous stroke or transient ischemic attack	24/846 (2.8)	21/850 (2.5)	151/549 (28)	132/544 (24)
At least mild cognitive impairment	319/797 (40)	305/819 (37)	263/529 (50)	279/522 (53)
Arterial hypertension	709/843 (84)	703/850 (83)	518/547 (95)	517/544 (95)
Systolic blood pressure, mm Hg	137 (19.1)	136 (19.3)	136 (19.9)	139 (19.2)
Diastolic blood pressure, mm Hg	82 (11.8)	82 (12.1)	79 (12.4)	81 (11.8)
Stable heart failure	161/846 (19)	161/850 (19)	235/549 (43)	241/544 (44)
Chronic kidney disease of MDRF stage 3 or 4	68/846 (8.0)	62/850 (7.3)	104/549 (19)	117/544 (22)
Diabetes	131/843 (16)	128/850 (15)	220/547 (40)	215/544 (40)
Severe coronary artery disease (previous MI, CABG, or PCI)	76/846 (9.0)	69/850 (8.1)	167/549 (30)	167/544 (31)
LVEF	59.5 (8.9)	59.7 (9.6)	57.8 (10.8)	57.3 (11.1)
Diastolic left atrium diameter (maximal diameter), mm	43.7 (8.6)	44.0 (8.7)	43.9 (8.1)	43.9 (8.3)
MoCA	25.9 (3.5)	26.1 (3.4)	24.8 (4.0)	24.5 (4.1)
EQ-5D score	74.0 (16.5)	74.2 (16.2)	68.0 (16.2)	67.5 (16.9)
SF-12 mental score	50.4 (9.9)	50.6 (9.7)	50.2 (9.8)	49.2 (10.0)
SF-12 physical score	46.2 (8.4)	46.2 (8.4)	42.2 (8.6)	42.1 (8.4)
Medication at discharge				
Oral anticoagulation with NOAC or VKA	755/842 (90)	755/849 (89)	512/547 (94)	495/544 (91)
Digoxin or digitoxin	27/842 (3.2)	44/849 (5.2)	19/547 (3.5)	41/544 (7.5)
β-blocker	636/842 (76)	717/849 (84)	422/547 (77)	474/544 (87)
ACE inhibitors or angiotensin II receptor blocker	529/842 (63)	548/849 (65)	424/547 (78)	431/544 (79)
Mineralocorticoid receptor antagonist	26/842 (3.1)	34/849 (4.0)	64/547 (12)	58/544 (11)
Diuretic	271/842 (32)	272/849 (32)	288/547 (53)	289/544 (53)
Statin	301/842 (36)	273/849 (32)	327/547 (60)	295/544 (54)
Platelet inhibitor	105/842 (12)	109/849 (13)	124/547 (23)	117/544 (22)
Oral antihyperglycemics	89/842 (11)	88/849 (10)	139/547 (25)	143/544 (26)
Planned therapy for rhythm control at baseline				
AAD	731/846 (86)	37/850 (4.4)	480/549 (87)	20/544 (3.7)
Catheter ablation	70/846 (8.3)	2/850 (0.2)	42/549 (7.7)	0/544 (0)
None	45/846 (5.3)	811/850 (95)	27/549 (4.9)	524/544 (96)

Values are mean (SD), n/total n (%), or median (interquartile range). There were no imbalances between randomized groups in the 2 strata (additional data available in Table S1). Patients with CHA_2DS_2-VASc score ≥4 were enriched for the components of the score. AAD indicates antiarrhythmic drug; ACE, angiotensin-converting enzyme; AF, atrial fibrillation; CABG, coronary artery bypass graft; EQ-5D, European Quality of Life–5 Dimensions; ERC, early rhythm control; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MoCA, Montreal Cognitive Assessment; NOAC, non–vitamin K antagonist oral anticoagulant; PCI, percutaneous coronary intervention; SF-12, 12-Item Short Form Health Survey; UC, usual care; and VKA, vitamin K antagonist.

Effects of ERC on the Primary Outcome by CHA_2DS_2-VASc Score Groups

ERC reduced the composite primary efficacy outcome of cardiovascular death, stroke, or hospitalization for worsening of HF or for acute coronary syndrome in patients with CHA_2DS_2-VASc score ≥4 (ERC, 127/549 patients with events; UC, 183/544; HR, 0.64 [0.51–0.81]; $P<0.001$), but not in patients with CHA_2DS_2-VASc score <4 (ERC, 122/846 patients with events; UC, 133/850; HR, 0.93 [0.73–1.19]; $P=0.56$; Figure 2A and 2B; $P_{interaction}=0.037$). The direction of each component of the primary outcome was consistent with the main finding (Table 2).

Effect on Nights Spent in Hospital (Second Primary Outcome Measure)

Patients with high CHA_2DS_2-VASc score spent more nights in the hospital (high CHA_2DS_2-VASc score: ERC, 7.37±23 nights spent in hospital/year; UC, 7.09±20.3 nights spent in hospital/year; $P=0.37$) than patients with lower CHA_2DS_2-VASc score (ERC, 4.83±21.2 nights spent in hospital/year; UC, 3.77±11.3 nights spent in hospital/year; $P=0.44$; Table S2). The effect of ERC on nights spent in the hospital was not different between the CHA_2DS_2-VASc strata ($P_{interaction}=0.97$).

Modeled Primary Outcome of Death, Disabling Stroke, Serious Bleeding, or Cardiac Arrest According to CHA_2DS_2-VASc Score Groups

A CABANA-like outcome was modeled with a combined primary end point of death, disabling stroke, serious bleeding, or cardiac arrest. This outcome behaved in a similar way as the primary outcome of EAST-AFNET4, showing effectiveness of ERC in patients with a CHA_2DS_2-VASc score ≥4 (ERC, 84/549 [15.3%] patients with events; UC, 118/544 [21.7%] patients with events; $P=0.009$), whereas in patients with a CHA_2DS_2-VASc score <4, no difference between ERC or UC was observed (ERC, 78/846 [9.2%] patients with events; UC, 73/850 [8.6%] patients with events; $P=0.532$, $P_{interaction}=0.028$).

Primary Safety Outcomes According to CHA_2DS_2-VASc Score and Age

The primary safety outcome (death, stroke, or serious adverse events of rhythm control therapy) was not different between study groups in patients with CHA_2DS_2-VASc score ≥4 (ERC, 112/549 patients with events; UC, 132/544 patients with events; HR, 0.84 [0.65, 1.08]; $P=0.175$), but occurred more often in patients with lower CHA_2DS_2-VASc scores randomized to ERC (ERC, 119/846 patients with events; UC, 91/850 patients with events; HR, 1.39 [1.05–1.82]; $P=0.019$, $P_{interaction}=0.008$). Overall, there was a constant rate of serious adverse events related to rhythm control of ≈1%/year (4.8% to 4.9% over the 5-year follow-up; Table 3) in both CHA_2DS_2-VASc score strata. The number of deaths and strokes was lower in patients with CHA_2DS_2-VASc scores <4 (Table 3). Because not all serious adverse events related to AF therapy were life-threatening, the number of patients experiencing death or a life-threatening event was counted. This analysis also excluded strokes because these are counted in the primary efficacy outcome. The number of patients with life-threatening events was not different between groups (low comorbidity burden: ERC, 72 patients with events; UC, 72 patients with events; high comorbidity burden: ERC, 82 patients with events; UC, 96 patients with events, $P_{interaction}=0.348$; Table S3).

Delivery of ERC and Frequency of Sinus Rhythm

Rhythm control therapy was initiated in a similar proportion of patients in both CHA_2DS_2-VASc strata and similar proportions of patients randomized to UC receiving rhythm control therapy (Figure 1, Table 1, and Table S4). Amiodarone was used more often in patients with CHA_2DS_2-VASc ≥4, whereas AF ablation was used more often in patients with a lower CHA_2DS_2-VASc score (Figure 1).

ERC therapy increased the proportion of patients in sinus rhythm at the end of the 2-year follow-up in both CHA_2DS_2-VASc strata. A higher number of patients in sinus rhythm was observed in the lower CHA_2DS_2-VASc stratum in both treatment groups (Table 4).

Quality of Life and Cognitive Function

Baseline quality of life was lower in patients with a higher comorbidity burden (Table 1). Quality of life at 2 years, assessed by the European Quality of Life–5 Dimensions visual analog scale, improved more in patients randomized to ERC in the higher CHA_2DS_2-VASc group than in patients randomized to UC (Table 4). There was no effect of randomized therapy on quality of life in patients with a lower CHA_2DS_2-VASc score <4 (Table 4). AF symptoms improved in both CHA_2DS_2-VASc strata without significant differences between randomized groups. At least mild cognitive impairment was observed more often in patients with higher CHA_2DS_2-VASc score (542/1051 [52%] patients) as compared with patients with lower CHA_2DS_2-VASc score (624/1616 [39%] patients; $P<0.001$). Similar changes in the Montreal Cognitive Assessment score were observed in both CHA_2DS_2-VASc strata (Table 4). Secondary outcomes without imputation are given in Table S5.

Table 2. Efficacy of Early Rhythm Control and Usual Care by Randomized Group and by CHA_2DS_2-VASc Score

Outcome	Lower comorbidity burden (CHA_2DS_2-VASc score <4)				Higher comorbidity burden (CHA_2DS_2-VASc score ≥4)				$P_{interaction}$
	ERC	UC	HR (95% CI)	*P* value	ERC	UC	HR (95% CI)	*P* value	
First primary outcome*	122/846 (14.4)	133/850 (15.6)	0.93 (0.73, 1.19)	0.562	127/549 (23.1)	183/544 (33.6)	0.64 (0.51, 0.81)	<0.001	0.037
Components of the first primary outcome									
Death from cardiovascular causes	30/846 (3.5)	35/850 (4.1)	0.88 (0.54, 1.44)	0.616	37/549 (6.7)	59/544 (10.8)	0.6 (0.4, 0.91)	0.015	0.252
Stroke	21/846 (2.5)	19/850 (2.2)	1.14 (0.61, 2.12)	0.683	19/549 (3.5)	43/544 (7.9)	0.43 (0.25, 0.74)	0.002	0.021
Hospitalization with worsening of HF	62/846 (7.3)	71/850 (8.4)	0.88 (0.62, 1.24)	0.464	77/549 (14)	98/544 (18)	0.74 (0.55, 1)	0.048	0.438
Hospitalization with ACS	27/846 (3.2)	35/850 (4.1)	0.8 (0.48, 1.31)	0.371	26/549 (4.7)	30/544 (5.5)	0.83 (0.49, 1.41)	0.495	0.853
Second primary outcome: nights spent in hospital/y	4.83±21.2	3.77±11.3	1.07 (0.9, 1.27)	0.442	7.37±23	7.09±20.3	1.09 (0.9, 1.33)	0.366	0.972
Other									
CABANA-like outcome	78/846 (9.2)	73/850 (8.6)	1.11 (0.8, 1.53)	0.532	84/549 (15.3)	118/544 (21.7)	0.69 (0.52, 0.91)	0.009	0.028

ACS indicates acute coronary syndrome; CABANA, Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation; ERC, early rhythm control; HF, heart failure; HR, hazard ratio; and UC, usual care.

*Composite of cardiovascular death, stroke, or hospitalization for worsening of HF or for ACS.

Interaction of Age With ERC Therapy

Because age contributes up to 2 points of the CHA_2DS_2-VASc score, exploratory analyses of age categories were performed. Age did not interact with ERC with regard to the primary outcome (age <65 years: ERC, 36/306 [11.8%] patients with events; UC, 42/279 [15.1%] patients with events; HR, 0.78 [0.5, 1.22]; *P*=0.282; age 65 to 74 years: ERC, 106/648 [16.4%] patients with events; UC, 132/663 [19.9%] patients with events; HR, 0.83 [0.64, 1.08]; *P*=0.165; age ≥75 years: ERC, 107/441 [24.3%] patients with events; UC, 142/452 [31.4%] patients with events; HR, 0.73 [0.64, 1.08]; *P*=0.017, $P_{interaction}$=0.687). Nights spent in hospital, the second primary outcome, occurred with similar frequency in ERC as compared with UC across the 3 different age groups (age <65 years: ERC, 4.7±22.5 days; UC, 2.66±5.5 days; HR, 1.21 [0.91, 1.6]; *P*=0.196; age 65 to 74 years: ERC, 5.01±18.8 days; UC, 4.5±12.2 days; HR, 1.12 [0.93, 1.35]; *P*=0.218; age ≥75 years: ERC, 7.82±25.7; UC, 7.37±22.3; HR, 1.07 [0.85, 1.34]; *P*=0.565, $P_{interaction}$=0.645). Splitting patients by age did not identify an interaction of age with the primary safety outcome (age <65 years: ERC, 26/306 [8.5%] patients with events; UC, 23/279 [8.2%] patients with events; HR, 1.12 [0.63, 1.98]; *P*=0.7; age 65 to 74 years: ERC, 95/648 [14.7%] patients with events; UC, 100/663 [15.1%] patients with events; HR, 1.02 [0.77, 1.35]; *P*=0.888; age ≥75 years: ERC, 110/441 [24.9%] patients with events; UC, 100/452 [22.1%] patients with events; HR, 1.16 [0.77, 1.35]; *P*=0.285, $P_{interaction}$=0.862). No differences in European Quality of Life–5 Dimensions score, 12-Item Short Form Health Survey physical or mental score, or Montreal Cognitive Assessment score were observed between age categories.

Additional Analyses: Eliminating Sex as a Risk Marker and Analyses Without Imputation

A growing body of evidence suggests that female sex contributes less than other components of the CHA_2DS_2-VASc score to risk prediction.[2,20,21] We therefore conducted a post hoc analysis comparing patients with a CHA_2DS_2-VA score ≥4 with those with a lower score. These analyses shifted more patients into the lower comorbidity group (ERC, 1008; UC, 1018), retaining ≈750 patients in the high-risk group (ERC, 387; UC, 376). In this CHA_2DS_2-VA <4 group, 175/1018 (17.2%) patients randomized to ERC experienced a first primary outcome event, not significantly different from the 143/1008 (14.2%) patients randomized to UC (HR, 0.83 [0.66, 1.04]; *P*=0.098). In patients with a CHA_2DS_2-VA ≥4, 106/387 patients (27.4%) randomized to ERC experienced a first primary outcome, less than the 141/376 patients (37.5%) randomized to UC (HR, 0.68 [0.53, 0.88]; *P*=0.003, $P_{interaction}$=0.250; Figure 2C and 2D). In the CHA_2DS_2-VA <4 group, 139/1018 patients (13.8%) randomized to ERC experienced a primary safety event, numerically more than the 120/1008 patients (11.8%) randomized to UC (HR, 1.23 [0.97, 1.58]; *P*=0.092). In patients with a high comorbidity burden excluding sex

Table 3. Primary Safety Outcomes by Randomized Group and by CHA_2DS_2-VASc Score

Outcome	Lower comorbidity burden (CHA_2DS_2-VASc score <4)				Higher comorbidity burden (CHA_2DS_2-VASc score ≥4)				$P_{interaction}$
	ERC	UC	HR (95% CI)	*P* value	ERC	UC	HR (95% CI)	*P* value	
Primary safety outcomes	119 (14.1)	91 (10.7)	1.39 (1.05, 1.82)	0.019	112 (20.4)	132 (24.3)	0.84 (0.65, 1.08)	0.1750	0.008
Death	66 (7.8)	70 (8.2)	0.97 (0.69, 1.36)	0.860	72 (13.1)	94 (17.3)	0.74 (0.54, 1.01)	0.0563	0.255
Stroke	21 (2.5)	19 (2.2)	1.14 (0.61, 2.12)	0.683	19 (3.5)	43 (7.9)	0.43 (0.25, 0.74)	0.0023	0.021
Serious adverse events related to rhythm control therapy, including:	41 (4.8)	14 (1.6)	3.11 (1.7, 5.72)	<0.001	27 (4.9)	5 (0.9)	5.51 (2.12, 14.3)	<0.001	0.337
Torsades de pointes	0 (0)	0 (0)	NA	NA	1 (0.2)	0 (0)	NA (0, Inf)	0.9997	0.998
Nonfatal cardiac arrest	0 (0)	0 (0)	NA	NA	1 (0.2)	1 (0.2)	1.03 (0.06, 16.4)	0.9856	>0.99
Drug toxicity related to AF treatment	7 (0.8)	2 (0.2)	3.57 (0.74, 17.19)	0.112	3 (0.5)	1 (0.2)	2.97 (0.31, 28.6)	0.3451	0.3451
Drug-induced bradycardia	9 (1.1)	4 (0.5)	2.34 (0.72, 7.61)	0.156	5 (0.9)	1 (0.2)	4.97 (0.58, 42.58)	0.1430	0.1430
Drug-induced atrioventricular block	2 (0.2)	0 (0)	NA (0, Inf)	>0.99	0 (0)	0 (0)	NA	NA	>0.99
Pericardial tamponade	1 (0.1)	0 (0.0)	NA (0, Inf)	>0.99	2 (0.4)	0 (0.0)	NA (0, Inf)	0.9996	>0.99
Major bleeding attributable to AF ablation	1 (0.1)	0 (0.0)	NA (0, Inf)	>0.99	5 (0.9)	0 (0.0)	NA (0, Inf)	0.9993	>0.99
Nonmajor bleeding attributable to AF ablation	1 (0.1)	2 (0.2)	0.55 (0.05, 6.06)	0.624	0 (0.0)	0 (0.0)	NA	NA	>0.99
Blood pressure–related event	1 (0.1)	0 (0.0)	NA (0, Inf)	>0.99	0 (0.0)	0 (0.0)	NA	NA	>0.99
Hospitalizations attributable to AF	8 (0.9)	1 (0.1)	8.33 (1.04, 66.68)	0.046	3 (0.5)	2 (0.4)	1.52 (0.25, 9.11)	0.6461	0.6461
Other cardiovascular event	3 (0.4)	1 (0.1)	3.16 (0.33, 30.44)	0.320	2 (0.4)	0 (0.0)	NA (0, Inf)	0.9994	0.997
Other event	0 (0.0)	2 (0.2)	0 (0, Inf)	>0.99	1 (0.2)	1 (0.2)	0.99 (0.06, 15.81)	0.9934	>0.99
Syncope	2 (0.2)	1 (0.1)	2.51 (0.22, 28.33)	0.455	2 (0.4)	0 (0.0)	NA (0, Inf)	0.9994	0.996
Hospitalization for worsening heart failure with decompensated heart failure	3 (0.4)	0 (0.0)	NA (0, Inf)	>0.99	0 (0.0)	0 (0.0)	NA	NA	>0.99
Implantation of a pacemaker, defibrillator, cardiac resynchronization device, or any other cardiac device	4 (0.5)	3 (0.4)	1.41 (0.31, 6.35)	0.652	4 (0.7)	1 (0.2)	3.95 (0.44, 35.3)	0.2196	0.438

All numbers are given as patients with events (annualized event rate). See text for details. AF indicates atrial fibrillation; ERC, early rhythm control; HR, hazard ratio; and UC, usual care.

(CHA_2DS_2-VA ≥4), 92/387 patients (23.8%) randomized to ERC experienced a primary safety event, not different from the 103/376 patients (27.4%) randomized to UC (HR, 0.87 [0.66, 1.16]; P=0.337, $P_{interaction}$=0.044). Details are given in Tables S6 and S7.

DISCUSSION

Main Findings

These prespecified subanalyses of EAST-AFNET4 show that systematic ERC therapy reduces cardiovascular complications compared with UC in patients with a high comorbidity burden, defined by a CHA_2DS_2-VASc score ≥4. ERC also improves quality of life in these patients. In patients with fewer comorbidities, reflected by CHA_2DS_2-VASc scores of 2 or 3, ERC therapy does not reduce outcomes compared with UC. Furthermore, an increase in serious adverse events related to rhythm control therapy, often attributable to bradycardia or drug toxicity, led to more primary safety outcomes in patients with lower CHA_2DS_2-VASc scores randomized to ERC, whereas the safety was balanced between randomized groups in patients with multiple comorbidities. The number of patients with life-threatening events was not different between randomized groups independent of comorbidity burden. These hypothesis-generating findings call for independent validation. Taken at face value, they support a preferential use of ERC in patients with a high comorbidity burden. Detailed analyses of adverse events related to AF therapy suggest that avoiding bradycardia and drug toxicity events on antiarrhythmic drug therapy, after AF

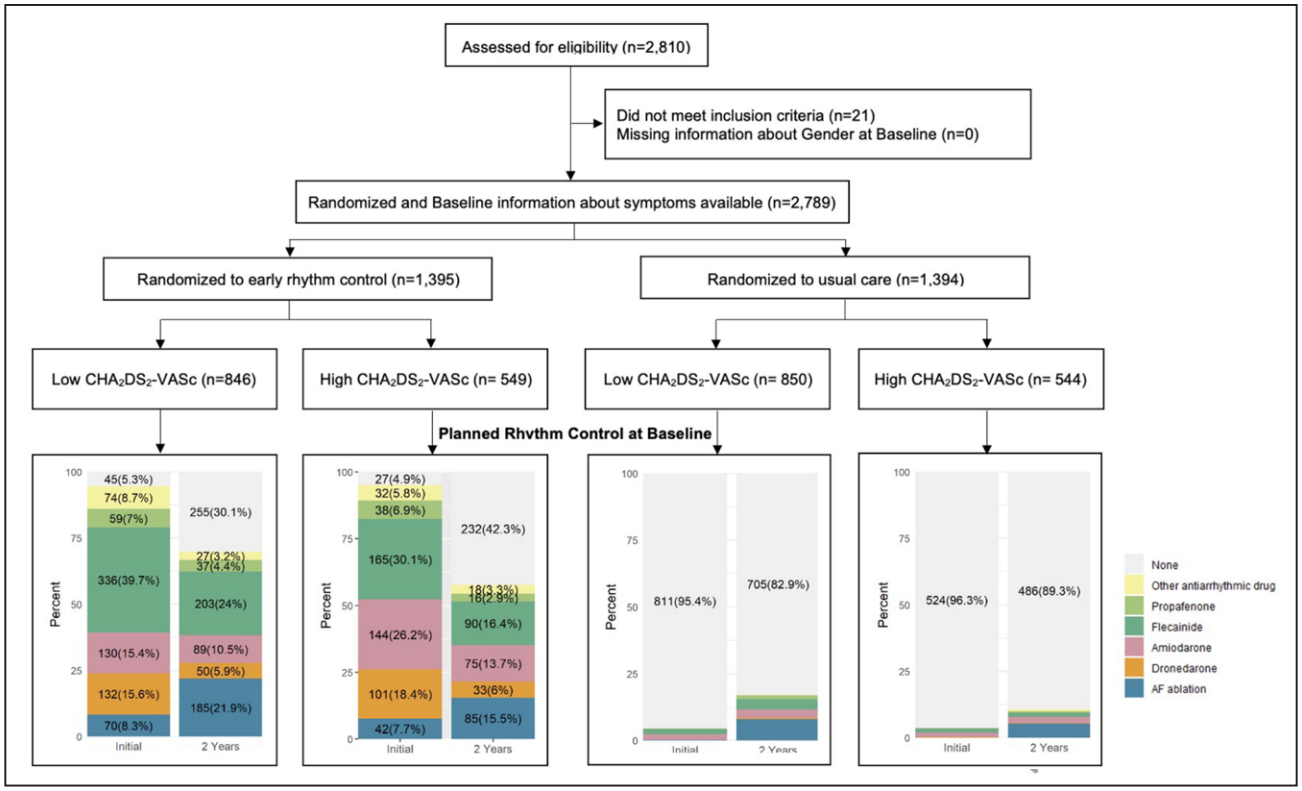

Figure 1. Consolidated standards of reporting trials flow chart of the prespecified analyses.
All patients were analyzed as randomized. AF indicates atrial fibrillation.

ablation, and without active rhythm control therapy could improve the safety of ERC in the future.

Interaction of a High CHA_2DS_2VASc Score With ERC Therapy

The CHA_2DS_2-VASc score is a combined score on the basis of the nonmodifiable risk factors age, female sex, and previous stroke and the potentially modifiable cardiovascular comorbidities hypertension, diabetes, HF, and vascular disease.[22] Comorbidities have a major effect on the risk of stroke and death in patients with AF.[15–17,23] It can therefore be expected that the risk of recurrent AF and the risk of AF-related cardiovascular complications is higher in patients with higher CHA_2DS_2-VASc scores.[24] It is commonly assumed that the risk of rhythm control therapy will also be higher in patients with multiple comorbidities. Our data show that ERC is especially effective in preventing cardiovascular complications in patients with multiple comorbidities (CHA_2DS_2-VASc score ≥4; Figure 2A). When sex is ignored as a risk factor (CHA_2DS_2-VA ≥4), similar trends are observed (Figure 2C and 2D), but the $P_{interaction}$ for efficacy is no longer significant. This underlines the importance of not withholding rhythm control therapy in patients with recently diagnosed AF and multiple comorbidities. These hypothesis-generating data call for a prospective randomized trial comparing rhythm control therapy with UC in patients with relatively recently diagnosed AF and higher CHA_2DS_2-VASc scores (≥4).

Treatment Type and Safety of ERC by CHA_2DS_2-VASc Score Strata

The frequency of patients who were randomized to UC and received rhythm control therapy at a later time point during the trial was comparable in randomized groups across all age groups and in higher or lower CHA_2DS_2-VASc score strata. Reflecting the higher prevalence of HF and vascular disease, amiodarone and dronedarone were more commonly used in patients with a CHA_2DS_2-VASc score ≥4 randomized to ERC (Figure 1). AF ablation was more commonly used in patients with lower CHA_2DS_2-VASc scores, reflecting clinical practice at the time. The outcomes of these analyses demonstrate that ERC therapy is feasible in patients of different ages and in particular in patients with multiple comorbidities. Rate control therapy was delivered in both randomized groups according to current guidelines[20] and distribution did not differ between patients with a higher or lower CHA_2DS_2-VASc score (Table 1 and Table S2). The detailed analyses of the safety outcomes related to rhythm control therapy indicate that life-threatening events are balanced equally across all 4 groups analyzed here (Table S4) and that bradycardia and drug toxicity–related events contribute importantly to the safety outcome, in both groups, but

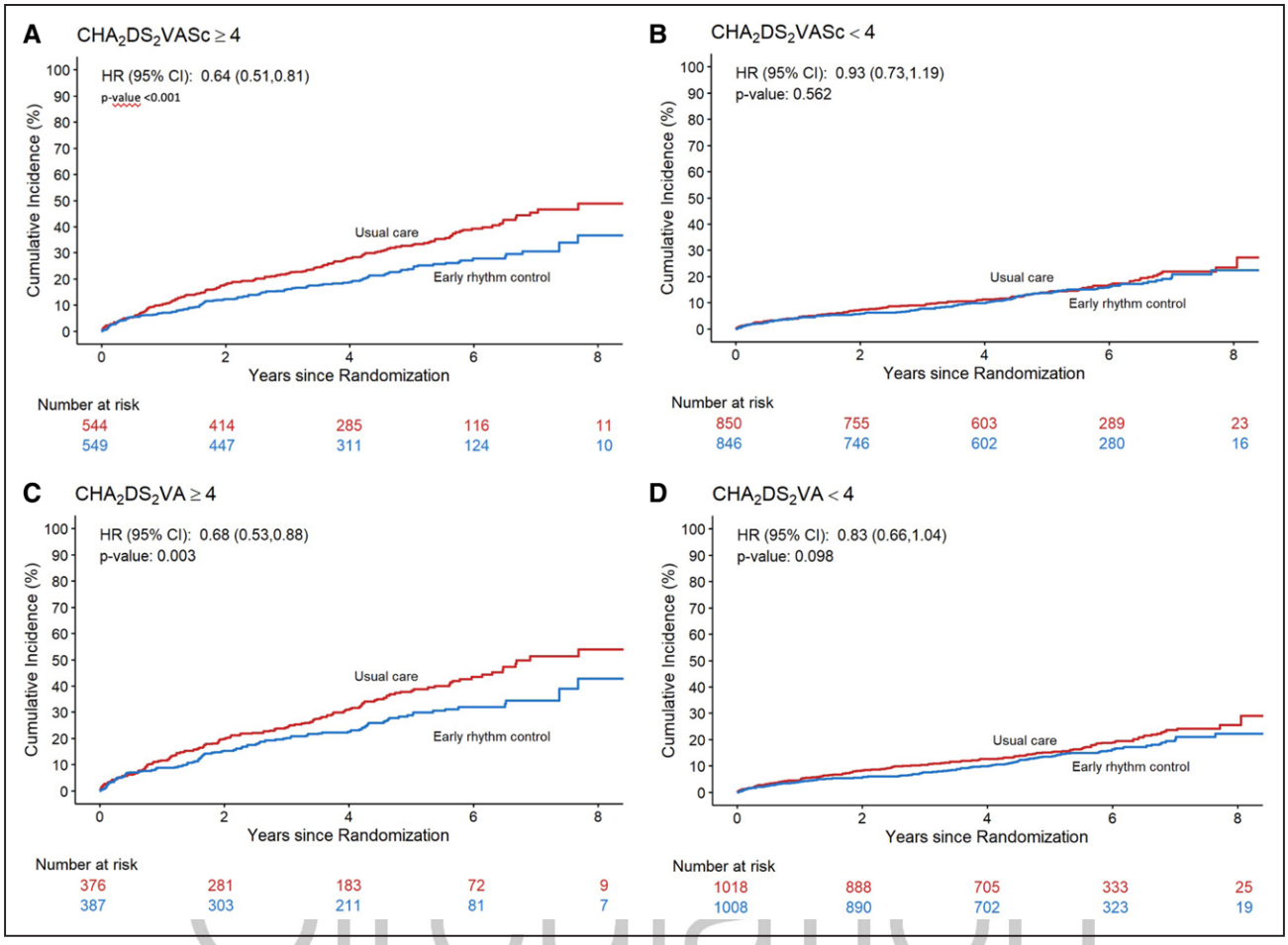

Figure 2. Effect of early rhythm control on the first primary outcome of EAST-AFNET4.
Effect of early rhythm control on the first primary outcome of EAST-AFNET4 (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial–Atrial Fibrillation Network), shown separately for patients with a high comorbidity burden (**A**, CHA_2DS_2-VASc score ≥4) and lower comorbidity burden (**B**, CHA_2DS_2-VASc score <4). Groups were split by a modified risk score ignoring sex as a risk factor and dividing them into patients with a high comorbidity burden (**C**, CHA_2DS_2-VA score ≥4) and a lower comorbidity burden (**D**, CHA_2DS_2-VA score <4). Shown are Aalen-Johansen curves indicating the time to a first cardiovascular death, stroke, hospitalization for heart failure, or hospitalization for acute coronary syndrome. HR indicates hazard ratio.

were generally more frequent in patients with low comorbidity burden (Table 3).

Effect of Age and Sex

Age is an important nonmodifiable risk factor for AF,[15] a component of the CHA_2DS_2-VASc score, and associated with mortality and cardiovascular events.[25] We therefore analyzed the effect of age on efficacy and safety outcomes in EAST-AFNET4 and found no interaction. There is no interaction of HF or symptoms on the primary efficacy or safety outcome of EAST-AFNET4.[4,5] Our results demonstrate clearly that ERC can be delivered safely across all ages studied in the trial. The sensitivity analyses ignoring sex as a risk factor support that rhythm control should not be withheld from women on the basis of their sex, aligned with the sex subanalyses in CABANA.[19] Dedicated randomized trials will be needed to better understand the effectiveness of AF ablation in younger patients observed in CABANA subanalyses[19] in context with the lack of interaction between age and outcomes in EAST-AFNET4 shown here.

Safety Aspects

Safety concerns are one of the main reasons to withhold rhythm control therapy in clinical practice.[26] The main results of EAST-AFNET4 have challenged this approach and call for a wider use of rhythm control therapy in patients with recently diagnosed AF. The results of the safety outcomes in these subanalyses provide more granularity to the safety of ERC therapy and yield 2 hypothesis-generating findings. The long-term complications of rhythm control therapy occur with similar frequency in patients with fewer and more comorbidities (≈5% over 5 years, or 1% per year, in both CHA_2DS_2-VASc strata; Table 3). This is comparable to the safety of anticoagulation therapy.[27–30] Total mortality

Table 4. Key Secondary Outcomes by Randomized Group and by CHA_2DS_2-VASc Score

Key secondary outcomes at 2 years	Lower comorbidity burden (CHA_2DS_2-VASc score <4)				Higher comorbidity burden (CHA_2DS_2-VASc score ≥4)				$P_{interaction}$
	ERC	UC	Adjusted difference/OR	*P* value	ERC	UC	Adjusted difference/OR	*P* value	
Change in LVEF	1.36±9.5	0.61±9.3	0.16 (−0.66, 0.97)	0.707	1.71±10.1	1.01±10.7	0.33 (−0.83, 1.48)	0.58	0.783
Change in EQ-5D score	0.53±17.4	0.47±16.4	−0.35 (−2.46, 1.76)	0.745	2.85±17.6	1.21±17.4	3.47 (0.38, 6.56)	0.028	0.042
Change in SF-12 mental score	0.67±10.6	1.33±9.8	−1.31 (−2.29, −0.32)	0.009	0.78±10.8	2.02±10.8	−1.01 (−2.44, 0.42)	0.166	0.734
Change in SF-12 physical score	0.46±8.5	0.28±7.8	0.18 (−0.71, 1.07)	0.694	0±8.5	−0.35±8.8	0.62 (−0.58, 1.83)	0.309	0.561
Change in MoCA score	0.231±3.2	−0.003±3.1	−0.002 (−0.3, 0.29)	0.987	−0.099±3.4	0.297±3.4	−0.35 (−0.81, 0.12)	0.144	0.218
Sinus rhythm at 2 years	587/846 (69.4)	458/850 (53.9)	3.24 (2.44, 4.3)	<0.001	334/549 (60.8)	229/544 (42.1)	3.1 (2.27, 4.25)	<0.001	0.873
Asymptomatic at 2 years	549/846 (64.9)	557/850 (65.5)	1.1 (0.84, 1.42)	0.495	312/549 (56.8)	293/544 (53.9)	1.22 (0.9, 1.66)	0.204	0.636

Effects are given as baseline-adjusted differences with 95% CIs for continuous outcomes and baseline-adjusted odds ratios (ORs) with 95% CIs for dichotomous outcomes. EQ-5D indicates European Quality of Life–5 Dimensions; ERC, early rhythm control; LVEF, left ventricular ejection fraction; MoCA, Montreal Cognitive Assessment; SF-12, 12-Item Short Form Health Survey; and UC, usual care.

and life-threatening adverse events (Table S4) were not different between groups. Second, and potentially counterintuitively, rhythm control was associated with a better net clinical benefit in patients with recently diagnosed AF and multiple comorbidities compared with patients with fewer comorbidities. This results from a clear reduction of cardiovascular complications in patients with multiple comorbidities. In patients with a lower comorbidity burden, a much smaller effect on stroke and death combines with a low but relevant incidence of complications related to rhythm control to create a clear safety signal without differences in stroke or total mortality between treatment groups (Table 3 and Table S4). A similar proportion of therapy-related safety events combined with a clear reduction in strokes and other efficacy outcomes leads to favorable clinical effects in patients with a high comorbidity burden. A key driver of the interaction between comorbidity strata and ERC was the reduction in strokes in patients with high comorbidity burden that was not observed in the low comorbidity stratum because of a very low number of events in both treatment groups (Table 3).

Perspectives for Research and Clinical Practice

Our analysis identified 2 novel aspects of ERC therapy. First, the risk of serious adverse events related to ERC was similar in patients with a higher or lower comorbidity burden. Whether innovations in AF ablation, a better selection of antiarrhythmic drugs, a more careful adaptation of rate control therapy, or other measures can improve the safety of ERC therapy remains to be tested in future studies.

Second, ERC mainly prevents AF-related complications in patients with multiple comorbidities, suggesting a synergistic interaction between AF and comorbidities that does not appear to be driven by age alone. One explanation could be that AF leads to stroke, cardiovascular death, HF hospitalizations, or acute coronary syndrome in the presence of additional atrial or ventricular cardiomyopathy and vascular damage. Pending verification in translational and clinical research, our data suggest that AF interacts with atrial cardiomyopathy or endothelial damage to lead to complications of AF.[31] Another explanation could be that patients with high comorbidity burden experience more and longer AF recurrences, thus enhancing the effect of ERC therapy on AF burden–related complications compared with UC in that stratum. Our analyses are hypothesis-generating. Our findings have 4 consequences:

1. Taken at face value, our data underpin the preferential use of ERC in patients with a high comorbidity burden.
2. Research analyzing the interaction between rhythm control therapy and comorbidities integrating detailed cardiovascular phenotyping and AF burden is needed to understand the interaction of comorbidity burden and rhythm control.
3. Safer methods to deliver rhythm control therapy need to be developed, informing future studies of rhythm control in patients with fewer comorbidities.
4. Adequately powered trials addressing the effectiveness and safety of ERC in patients with AF and multiple comorbidities, and possibly in patients with AF after an acute stroke, are needed.

Limitations and Strengths

Whereas these were prespecified subanalyses of the randomized EAST-AFNET4, the subgroups compared here are not large enough to be sufficiently powered. The results are therefore hypothesis-generating. Our findings call for independent, randomized trials testing methods of ERC therapy in patients with relatively recently diagnosed AF and lower or higher cardiovascular comorbidity burden.

Conclusions

On the basis of these subanalyses of EAST-AFNET4, patients with recently diagnosed AF and multiple cardiovascular comorbidities should have rapid, priority access to rhythm control therapy to reduce cardiovascular outcomes. The safety signal identified in these analyses highlights the need to develop safer ways to deliver ERC, especially in patients with few cardiovascular conditions, including techniques avoiding bradycardia-related events, AF hospitalizations, and drug toxicity. Specific trials are warranted to validate our hypothesis-generating findings.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S7

REFERENCES

1. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J.* 2021;42:373–498. doi: 10.1093/eurheartj/ehaa612
2. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the Heart Rhythm Society in collaboration with the Society of Thoracic Surgeons. *Circulation.* 2019;140:e125–e151. doi: 10.1161/CIR.0000000000000665
3. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, Fetsch T, van Gelder IC, Haase D, Haegeli LM, et al. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med.* 2020;383:1305–1316. doi: 10.1056/NEJMoa2019422
4. Rillig A, Magnussen C, Ozga AK, Suling A, Brandes A, Breithardt G, Camm AJ, Crijns H, Eckardt L, Elvan A, et al. Early rhythm control therapy in patients with atrial fibrillation and heart failure. *Circulation.* 2021;144:845–858. doi: 10.1161/CIRCULATIONAHA.121.056323
5. Willems S, Borof K, Brandes A, Breithardt G, Camm AJ, Crijns H, Eckardt L, Gessler N, Goette A, Haegeli LM, et al. Systematic, early rhythm control strategy for atrial fibrillation in patients with or without symptoms: the EAST-AFNET 4 trial. *Eur Heart J.* 2021;43:1219–1230. doi: 10.1093/eurheartj/ehab593
6. Connolly SJ, Crijns HJ, Torp-Pedersen C, van Eickels M, Gaudin C, Page RL, Hohnloser SH. Analysis of stroke in ATHENA: a placebo-controlled, double-blind, parallel-arm trial to assess the efficacy of dronedarone 400 mg BID for the prevention of cardiovascular hospitalization or death from any cause in patients with atrial fibrillation/atrial flutter. *Circulation.* 2009;120:1174–1180. doi: 10.1161/CIRCULATIONAHA.109.875252
7. Hohnloser SH, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C, Connolly SJ. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med.* 2009;360:668–678. doi: 10.1056/NEJMoa0803778
8. Friberg L, Tabrizi F, Englund A. Catheter ablation for atrial fibrillation is associated with lower incidence of stroke and death: data from Swedish health registries. *Eur Heart J.* 2016;37:2478–2487. doi: 10.1093/eurheartj/ehw087
9. Tscholl V, Lin T, Lsharaf AK, Bellmann B, Nagel P, Lenz K, Landmesser U, Roser M, Rillig A. Cryoballoon ablation in the elderly: one year outcome and safety of the second-generation 28mm cryoballoon in patients over 75 years old. *Europace.* 2018;20:772–777. doi: 10.1093/europace/eux128

10. Heeger CH, Bellmann B, Fink T, Bohnen JE, Wissner E, Wohlmuth P, Rottner L, Sohns C, Tilz RR, Mathew S, et al. Efficacy and safety of cryoballoon ablation in the elderly: a multicenter study. *Int J Cardiol.* 2019;278:108–113. doi: 10.1016/j.ijcard.2018.09.090
11. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J.* 2016;37:2893–2962. doi: 10.1093/ejcts/ezw313
12. Connolly SJ, Camm AJ, Halperin JL, Joyner C, Alings M, Amerena J, Atar D, Avezum A, Blomstrom P, Borggrefe M, et al. Dronedarone in high-risk permanent atrial fibrillation. *N Engl J Med.* 2011;365:2268–2276. doi: 10.1056/NEJMoa1109867
13. Lee WC, Wu PJ, Chen HC, Fang HY, Liu PY, Chen MC. Efficacy and safety of ablation for symptomatic atrial fibrillation in elderly patients: a meta-analysis. *Front Cardiovasc Med.* 2021;8:734204. doi: 10.3389/fcvm.2021.734204
14. Kawamura I, Aikawa T, Yokoyama Y, Takagi H, Kuno T. Catheter ablation for atrial fibrillation in elderly patients: systematic review and a meta-analysis. *Pacing Clin Electrophysiol.* 2022;45:59–71. doi: 10.1111/pace.14413
15. Kornej J, Borschel CS, Benjamin EJ, Schnabel RB. Epidemiology of atrial fibrillation in the 21st century: novel methods and new insights. *Circ Res.* 2020;127:4–20. doi: 10.1161/CIRCRESAHA.120.316340
16. Harb SC, Wang TKM, Nemer D, Wu Y, Cho L, Menon V, Wazni O, Cremer PC, Jaber W. CHA2DS2-VASc score stratifies mortality risk in patients with and without atrial fibrillation. *Open Heart.* 2021;8:e001794. doi: 10.1136/openhrt-2021-001794
17. Gazova A, Leddy JJ, Rexova M, Hlivak P, Hatala R, Kyselovic J. Predictive value of CHA2DS2-VASc scores regarding the risk of stroke and all-cause mortality in patients with atrial fibrillation (CONSORT compliant). *Medicine.* 2019;98:e16560. doi: 10.1097/MD.0000000000016560
18. Metzner A, Suling A, Brandes A, Breithardt G, Camm AJ, Crijns H, Eckardt L, Elvan A, Goette A, Haegeli LM, et al. Anticoagulation, therapy of concomitant conditions, and early rhythm control therapy: a detailed analysis of treatment patterns in the EAST-AFNET 4 trial. *Europace.* 2022;24:552–564. doi: 10.1093/europace/euab277
19. Bahnson TD, Giczewska A, Mark DB, Russo AM, Monahan KH, Al-Khalidi HR, Silverstein AP, Poole JE, Lee KL, Packer D. Association between age and outcomes of catheter ablation versus medical therapy for atrial fibrillation: results from the CABANA trial. *Circulation.* 2021;145:796–804. doi: 10.1161/CIRCULATIONAHA.121.055297
20. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2021;42:373–498. doi: 10.1093/eurheartj/ehaa612
21. Friberg L, Benson L, Rosenqvist M, Lip GY. Assessment of female sex as a risk factor in atrial fibrillation in Sweden: nationwide retrospective cohort study. *BMJ.* 2012;344:e3522. doi: 10.1136/bmj.e3522
22. Olesen JB, Fauchier L, Lane DA, Taillandier S, Lip GYH. Risk factors for stroke and thromboembolism in relation to age among patients with atrial fibrillation: the Loire Valley Atrial Fibrillation Project. *Chest.* 2012;141:147–153. doi: 10.1378/chest.11-0862
23. Chung MK, Eckhardt LL, Chen LY, Ahmed HM, Gopinathannair R, Joglar JA, Noseworthy PA, Pack QR, Sanders P, Trulock KM, et al; Secondary Prevention Committee of the Council on Clinical Cardiology. Lifestyle and risk factor modification for reduction of atrial fibrillation: a scientific statement from the American Heart Association. *Circulation.* 2020;141:e750–e772. doi: 10.1161/CIR.0000000000000748
24. Morrone D, Kroep S, Ricci F, Renda G, Patti G, Kirchhof P, Chuang LH, van Hout B, De Caterina R. Mortality prediction of the CHA2DS2-VASc score, the HAS-BLED score, and their combination in anticoagulated patients with atrial fibrillation. *J Clin Med.* 2020;9. doi: 10.3390/jcm9123987
25. Ganna A, Ingelsson E. 5 year mortality predictors in 498 103 UK Biobank participants: a prospective population-based study. *Lancet.* 2015;386:533–540. doi: 10.1016/S0140-6736(15)60175-1
26. Camm A, Naccarelli G, Mittal S, Crijns H, Hohnloser S, Ma CS, Natale A, Turakhia M, Kirchhof P. Increasing role of rhythm control in patients with atrial fibrillation. *J Am Coll Cardiol.* 2022;79:1932–1948. doi: 10.1016/j.jacc.2022.03.337
27. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet.* 2014;383:955–962. doi: 10.1016/S0140-6736(13)62343-0
28. Kirchhof P, Radaideh G, Kim YH, Lanas F, Haas S, Amarenco P, Turpie AGG, Bach M, Lambelet M, Hess S, et al. Global prospective safety analysis of rivaroxaban. *J Am Coll Cardiol.* 2018;72:141–153. doi: 10.1016/j.jacc.2018.04.058
29. de Groot JR, Weiss TW, Kelly P, Monteiro P, Deharo JC, de Asmundis C, Lopez-de-Sa E, Waltenberger J, Steffel J, Levy P, et al. Edoxaban for stroke prevention in atrial fibrillation in routine clinical care: 1-year follow-up of the prospective observational ETNA-AF-Europe study. *Eur Heart J Cardiovasc Pharmacother.* 2021;7:f30–f39. doi: 10.1093/ehjcvp/pvaa079
30. Lopez-Lopez JA, Sterne JAC, Thom HHZ, Higgins JPT, Hingorani AD, Okoli GN, Davies PA, Bodalia PN, Bryden PA, Welton NJ, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. *BMJ.* 2017;359:j5058. doi: 10.1136/bmj.j5058
31. Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, Chugh SS, Corradi D, D'Avila A, Dobrev D, et al. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Europace.* 2016;18:1455–1490.