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Early Rhythm Control Therapy for Atrial Fibrillation in Low-Risk Patients

A Nationwide Propensity Score–Weighted Study

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Background: Rhythm control is associated with lower risk for adverse cardiovascular outcomes compared with usual care among patients recently diagnosed with atrial fibrillation (AF) with a CHA_2DS_2-VASc score of approximately 2 or greater in EAST-AFNET 4 (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial).

Objective: To investigate whether the results can be generalized to patients with low stroke risk.

Design: Population-based cohort study.

Setting: Nationwide claims database of the Korean National Health Insurance Service.

Participants: 54 216 patients with AF having early rhythm control (antiarrhythmic drugs or ablation) or rate control therapy that was initiated within 1 year of the AF diagnosis.

Measurements: The effect of early rhythm control on the primary composite outcome of cardiovascular death, ischemic stroke, hospitalization for heart failure, or myocardial infarction was compared between eligible and ineligible patients for EAST-AFNET 4 (CHA_2DS_2-VASc score, approximately 0 to 1) using propensity overlap weighting.

Results: In total, 37 557 study participants (69.3%) were eligible for the trial (median age, 70 years; median CHA_2DS_2-VASc score, 4), among whom early rhythm control was associated with lower risk for the primary composite outcome than rate control (hazard ratio, 0.86 [95% CI, 0.81 to 0.92]). Among the 16 659 low-risk patients (30.7%) who did not meet the inclusion criteria (median age, 54 years; median CHA_2DS_2-VASc score, 1), early rhythm control was consistently associated with lower risk for the primary outcome (hazard ratio, 0.81 [CI, 0.66 to 0.98]). No significant differences in safety outcomes were found between the rhythm and rate control strategies regardless of trial eligibility.

Limitation: Residual confounding.

Conclusion: In routine clinical practice, the beneficial association between early rhythm control and cardiovascular complications was consistent among low-risk patients regardless of trial eligibility.

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Atrial fibrillation (AF) is associated with increased risk for mortality and morbidity from stroke and congestive heart failure and impaired quality of life, even for patients who receive optimal anticoagulation and rate control treatment (1–4). Rate control is integral to the management of AF and often sufficiently improves the associated symptoms (1, 2). By restoring and maintaining sinus rhythm using antiarrhythmic drug treatment, cardioversion, and AF ablation, rhythm control ameliorates symptoms and improves quality of life (5). Several randomized trials, including the landmark AFFIRM (Atrial Fibrillation Follow-up Investigation of sinus Rhythm Management) trial, have compared rhythm control with rate control and showed no significant differences in effects on mortality and stroke (6–8). EAST-AFNET 4 (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial) recently showed that rhythm control therapy was associated with lower risk for adverse cardiovascular outcomes compared with usual care among patients diagnosed with AF within the previous year (9). The study included patients at risk for stroke (CHA_2DS_2-VASc score, approximately ≥2), but whether the results can be generalized to patients with low stroke risk is unclear. Although the primary indication for rhythm control is to alleviate AF-related symptoms and improve quality of life, the current guidelines suggest younger age and no or few comorbid conditions as factors favoring rhythm control. Thus, the effect of rhythm control on cardiovascular outcomes in this population requires elucidation.

This study aimed to translate the results of EAST-AFNET 4 into routine clinical practice. We examined the association between early rhythm control and cardiovascular outcomes stratified by trial eligibility compared with rate control.

Methods

This retrospective study was based on the claims database established by the National Health Insurance Service of Korea. The **Supplement** (available at Annals.org) provides further details. This study was approved by

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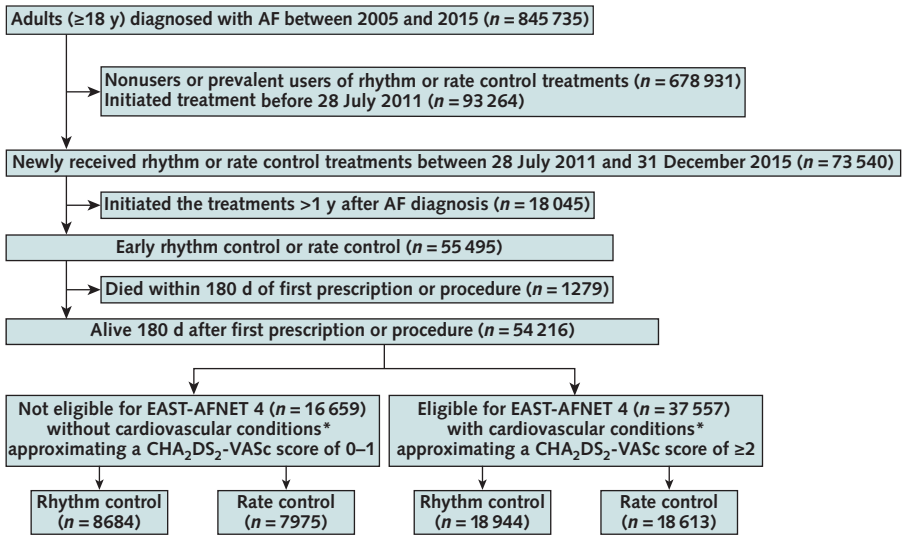
Figure 1. Study flow diagram.



AF = atrial fibrillation; EAST-AFNET 4 = Early Treatment of Atrial Fibrillation for Stroke Prevention Trial.
* Age >75 y, previous transient ischemic attack or stroke, or meets 2 of the following criteria: age >65 y, female sex, heart failure, hypertension, diabetes mellitus, history of myocardial infarction, and chronic kidney disease.

the institutional review board of the Yonsei University Health System (4-2016-0179), which waived the requirement for informed consent because personal identification information was removed after cohort generation in accordance with strict confidentiality guidelines.

Cohort Design and Study Population

Details of the study protocol are in **Supplement Table 1** (available at Annals.org). We identified adults (aged ≥18 years) with AF who were treated with rhythm control or rate control between 28 July 2011 and 31 December 2015. In EAST-AFNET 4, early treatment of AF was defined as initiation of rhythm or rate control treatment within 1 year after diagnosis. The trial defined AF according to the International Classification of Diseases, Tenth Revision, code I48. The diagnosis of AF was previously validated in the National Health Insurance Service database with a positive predictive value of 94.1% (10). We used a new-user design for the rhythm control or rate control treatments. New use was defined as having no prior record of prescriptions or procedures of interest in the database, including data from 1 January 2002. Rhythm control treatment was defined as a prescription for more than a 90-day supply of any rhythm control drug during the 180-day period since the first prescription or an ablation procedure for AF. Rate control treatment was defined as a prescription for more than a 90-day supply of any rate control drug during the 180-day period since the first prescription, with no prescription of rhythm control drug and no ablation in this period. A prescription of rhythm control drugs for more than 90 days or ablation within the 180-day period since the initiation of rate control therapy was classified as a rhythm control treatment. **Supplement Table 2** (available at Annals.org) shows rhythm control and rate control drugs and claim codes for ablation procedures.

This study excluded patients who died within 180 days of their first record of a prescription or procedure. We divided patients into the following 2 subgroups (**Figure 1**): those eligible for EAST-AFNET 4, who met at least 1 of 3 criteria (older than 75 years; history of transient ischemic attack or stroke; or at least 2 among age >65 years, female sex, heart failure, hypertension, diabetes mellitus, previous myocardial infarction, or chronic kidney disease), and those who did not meet the criteria—that is, stroke-free patients aged 75 years or younger with no or 1 stroke risk factor.

Outcome and Covariates

The primary outcome was a composite of death from cardiovascular causes, ischemic stroke, hospitalization due to heart failure, or acute myocardial infarction. We investigated individual components of the primary composite outcome and the number of nights spent in the hospital per year during the individual follow-up (the same end points as in EAST-AFNET 4) (9). The composite safety outcome comprised death due to any cause, bleeding (intracranial or gastrointestinal) requiring hospital admission, or prespecified serious adverse events of special interest indicating complications of the rhythm control treatment. **Supplement Table 3** (available at Annals.org) defines the outcomes in detail. Follow-up of the study outcomes was started 180 days after the first recorded prescription or procedure and lasted until the end of follow-up in the database (31 December 2016) or death. Each outcome was examined separately. The Methods section of the **Supplement** and **Supplement Table 2** provide details about the covariates.

Statistical Analysis

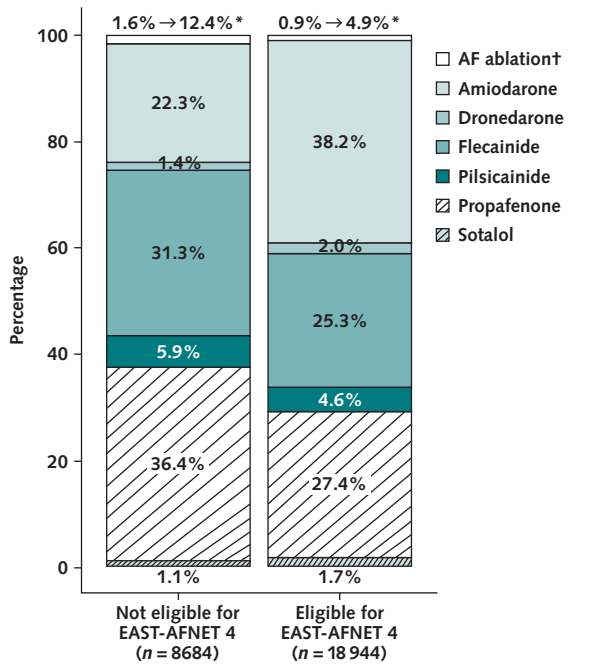
Statistical Methods

We used descriptive statistics to summarize the patients' baseline characteristics. Propensity overlap weighting was used to account for differences in the baseline characteristics between patients who had rhythm control and those who had rate control (11). The Methods section of the **Supplement** presents details of the propensity overlap weighting, and **Supplement Figure 1** (available at Annals.org) shows the distribution of propensity scores before and after weighting. The balance between the treatment populations was evaluated by standardized differences of all baseline covariates using a threshold of 0.1 to indicate imbalance. We calculated weighted incidence rates as the weighted number of clinical events during the follow-up period divided by 100 person-years at risk. The Methods section of the **Supplement** provides details about calculation of absolute rate differences between rhythm and rate control treatments. We compared the incidence of outcomes using the weighted log-rank test and plotted the weighted failure curves. The Fine–Gray competing risk regression was used to consider all-cause death as a competing event while estimating the relative hazards of the clinical outcomes (12). Cofactors that had not been balanced by weighting were included as covariates in the competing risk regression. The proportional hazards assumption was tested on the basis of Schoenfeld residuals (13). Findings for the analyses of secondary outcomes should be interpreted as exploratory because of the potential for type 1 error due to multiple comparisons. No data were missing in this study because we used only inpatient and outpatient hospital diagnoses and pharmacy claims and did not use laboratory variables or information from physical examination. Statistical analyses were done using SAS, version 9.3 (SAS Institute), and R, version 3.6.0 (R Foundation).

Sensitivity Analyses

We initially did subgroup analyses for the primary composite outcome stratified by sex, age, use of oral anticoagulants, level of care initiating the treatment, and CHA_2DS_2-VASc score. Interaction tests were done for all subgroups. We used the test variable from the weighting procedure to recreate the overlap weighting. Second, we further included all of the variables used in propensity score calculation as covariates in the competing risk regression models to adjust for residual imbalance after overlap weighting. Third, we did a time-varying regression wherein treatment (rhythm vs. rate control) was treated as a time-dependent variable considering switches between treatments (**Supplement Figure 2**, available at Annals.org). Fourth, we used 1:1 propensity score matching (without replacement and with a caliper of 0.01) instead of propensity overlap weighting. The balance of covariates after matching is shown in **Supplement Table 4** and **Supplement Figure 3** (available at Annals.org). Fifth, we defined the treatment strategies of rhythm or rate control as a prescription for more than a 20-day supply of the drugs in the 30-day period since the first prescription, instead of the 180-day period in the main analyses. Follow-up began 30 days after the first recorded prescription or procedure to avoid immortal time bias. Last, we did a "falsification analysis" to measure systematic bias in this study by using 30 prespecified falsification end points, with true hazard ratios (HRs) of 1 (14, 15). Detailed definitions of the falsification end points are presented in **Supplement Table 5** (available at Annals.org).

Figure 2. Initial choice of rhythm control treatment in patients recently (within 1 y) diagnosed with AF who did not meet the EAST-AFNET 4 inclusion criteria or who would be eligible for the trial.



AF = atrial fibrillation; EAST-AFNET 4 = Early Treatment of Atrial Fibrillation for Stroke Prevention Trial.

* Proportion of patients who eventually had catheter ablation for AF during the entire follow-up period.

† Ablation done within 180 d of the initial prescription of rhythm control drugs was classified as an initial choice of rhythm control.

Role of the Funding Source

This research was supported by the Ministry of Health and Welfare and the Ministry of Food and Drug Safety of the Republic of Korea, which had no role in study design; collection, analysis, or interpretation of data; writing of the report; or the decision to submit the manuscript for publication.

RESULTS

We identified 54 216 patients who had recently been diagnosed with AF (within 1 year) and were having rhythm control or rate control treatment. Of the study population, 16 659 participants (30.7%) did not meet the inclusion criteria (ineligible), whereas 37 557 (69.3%) were eligible for EAST-AFNET 4. Compared with ineligible patients, eligible patients were likely to be older (median age, 70 vs. 54 years); had higher CHA_2DS_2-

Table 1. Baseline Characteristics of Patients Not Eligible or Eligible for EAST-AFNET 4, According to Treatment Strategies Before Overlap Weighting*

Variable	Before Propensity Overlap Weighting					
	Did Not Meet Inclusion Criteria for EAST-AFNET 4 (*n* = 16 659)			Eligible for EAST-AFNET 4 (*n* = 37 557)		
	Rhythm Control (*n* = 8684)	Rate Control (*n* = 7975)	ASD, %	Rhythm Control (*n* = 18 944)	Rate Control (*n* = 18 613)	ASD, %
Median age (IQR), *y*	54 (47–60)	54 (47–61)	1.6	69 (61–75)	72 (63–78)	20.2
Male sex	7487 (86.2)	6457 (81.0)	14.2	9582 (50.6)	9579 (51.5)	1.8
High tertile of income	4191 (48.3)	2911 (36.5)	24.0	8731 (46.1)	7594 (40.8)	10.7
Median AF duration (IQR), *d*	1 (0–21)	0 (0–0)	25.7	0 (0–27)	0 (0–4)	17.2
Enrollment year						
2011	708 (8.2)	857 (10.7)	8.9	1369 (7.2)	1553 (8.3)	4.2
2012	1795 (20.7)	1960 (24.6)	9.3	3528 (18.6)	4044 (21.7)	7.7
2013	1941 (22.4)	1684 (21.1)	3.0	4077 (21.5)	4227 (22.7)	2.9
2014	2033 (23.4)	1714 (21.5)	4.6	4666 (24.6)	4169 (22.4)	5.3
2015	2207 (25.4)	1760 (22.1)	7.9	5304 (28.0)	4620 (24.8)	7.2
Risk scores						
CHA_2DS_2-VASc score	1 (0–1)	1 (0–1)	11.8	4 (2–5)	4 (2–5)	8.3
mHAS-BLED score†	1 (1–2)	1 (0–2)	13.1	3 (2–4)	3 (2–3)	17.7
Charlson Comorbidity Index	2 (1–3)	1 (0–2)	6.5	4 (2–6)	3 (2–5)	30.9
Hospital Frailty Risk Score	0.0 (0.0–2.1)	0.0 (0.0–2.4)	10.2	2.5 (0.0–6.4)	2.3 (0.0–6.5)	0.9
Medical history						
Heart failure	752 (8.7)	1111 (13.9)	16.7	8913 (47.0)	9165 (49.2)	4.4
History of admission owing to heart failure	142 (1.6)	265 (3.3)	10.9	1929 (10.2)	2239 (12.0)	5.9
Hypertension	2212 (25.5)	1326 (16.6)	21.8	15 893 (83.9)	12 544 (67.4)	39.2
Diabetes	308 (3.5)	294 (3.7)	0.7	5558 (29.3)	4705 (25.3)	9.1
Dyslipidemia	5340 (61.5)	4299 (53.9)	15.4	16 143 (85.2)	13 714 (73.7)	28.8
Ischemic stroke	0 (0.0)	0 (0.0)	<0.1	4959 (26.2)	4694 (25.2)	2.2
Transient ischemic attack	0 (0.0)	0 (0.0)	<0.1	2225 (11.7)	1640 (8.8)	9.7
Intracranial bleeding	50 (0.6)	110 (1.4)	8.2	493 (2.6)	523 (2.8)	1.3
Myocardial infarction	59 (0.7)	194 (2.4)	14.2	1953 (10.3)	1501 (8.1)	7.8
Peripheral arterial disease	426 (4.9)	359 (4.5)	1.9	3225 (17.0)	2195 (11.8)	14.9
Valvular heart disease	235 (2.7)	387 (4.9)	11.3	971 (5.1)	922 (5.0)	0.8
Chronic kidney disease	50 (0.6)	42 (0.5)	0.7	1622 (8.6)	1027 (5.5)	11.9
Proteinuria	367 (4.2)	358 (4.5)	1.3	1394 (7.4)	1166 (6.3)	4.3
Hyperthyroidism	736 (8.5)	825 (10.3)	6.4	2517 (13.3)	1602 (8.6)	15.0
Hypothyroidism	637 (7.3)	488 (6.1)	4.9	2760 (14.6)	1810 (9.7)	14.9
Cancer	1245 (14.3)	1153 (14.5)	0.3	4847 (25.6)	4316 (23.2)	5.6
COPD	1178 (13.6)	1098 (13.8)	0.6	6178 (32.6)	5814 (31.2)	3.0
Chronic liver disease	3147 (36.2)	2770 (34.7)	3.1	8636 (45.6)	7121 (38.3)	14.9
Hypertrophic cardiomyopathy	86 (1.0)	70 (0.9)	1.2	336 (1.8)	148 (0.8)	8.7
Osteoporosis	576 (6.6)	507 (6.4)	1.1	7359 (38.8)	6598 (35.4)	7.0
Sleep apnea	93 (1.1)	38 (0.5)	6.8	112 (0.6)	68 (0.4)	3.3
Concurrent medication‡						
Oral anticoagulant	3139 (36.1)	1565 (19.6)	37.5	9246 (48.8)	7077 (38.0)	21.9
Warfarin	2559 (29.5)	1445 (18.1)	26.9	7312 (38.6)	5881 (31.6)	14.7
NOAC	643 (7.4)	167 (2.1)	25.2	2471 (13.0)	1594 (8.6)	14.5
β-Blocker	3337 (38.4)	6101 (76.5)	83.4	9016 (47.6)	13 077 (70.3)	47.3
Nondihydropyridine CCB	1059 (12.2)	1243 (15.6)	9.8	2183 (11.5)	2821 (15.2)	10.7
Digoxin	259 (3.0)	1634 (20.5)	56.5	1212 (6.4)	5702 (30.6)	65.7
Aspirin	4453 (51.3)	3848 (48.3)	6.1	8504 (44.9)	8661 (46.5)	3.3
P2Y12 inhibitor	749 (8.6)	772 (9.7)	3.7	3427 (18.1)	3358 (18.0)	0.1
Statin	1969 (22.7)	2000 (25.1)	5.6	8407 (44.4)	7158 (38.5)	12.0
Dihydropyridine CCB	694 (8.0)	647 (8.1)	0.4	4394 (23.2)	2840 (15.3)	20.2
ACEI/ARB	2077 (23.9)	2372 (29.7)	13.2	9699 (51.2)	8982 (48.3)	5.9
Loop/thiazide diuretics	903 (10.4)	1899 (23.8)	36.2	6677 (35.2)	8586 (46.1)	22.3
Potassium-sparing diuretics	278 (3.2)	793 (9.9)	27.5	2039 (10.8)	3464 (18.6)	22.3
α-Blocker	94 (1.1)	67 (0.8)	2.5	443 (2.3)	401 (2.2)	1.2

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Table 1–Continued

Variable	Before Propensity Overlap Weighting					
	Did Not Meet Inclusion Criteria for EAST-AFNET 4 (*n* = 16 659)			Eligible for EAST-AFNET 4 (*n* = 37 557)		
	Rhythm Control (*n* = 8684)	Rate Control (*n* = 7975)	ASD, %	Rhythm Control (*n* = 18 944)	Rate Control (*n* = 18 613)	ASD, %
Level of health care initiating treatment						
Clinic	711 (8.2)	1349 (16.9)	26.6	1465 (7.7)	2812 (15.1)	23.3
Hospital	3306 (38.1)	3773 (47.3)	18.8	8272 (43.7)	9961 (53.5)	19.8
Tertiary referral hospital	4667 (53.7)	2853 (35.8)	36.7	9207 (48.6)	5840 (31.4)	35.7
Health care use						
≥12 outpatient visits per year	6029 (69.4)	5326 (66.8)	5.7	16 332 (86.2)	14 620 (78.5)	20.2
Area of residence						
Capital	4481 (51.6)	3825 (48.0)	7.3	9202 (48.6)	7816 (42.0)	13.3
Northeastern	176 (2.0)	298 (3.7)	10.2	638 (3.4)	898 (4.8)	7.4
Central	1122 (12.9)	647 (8.1)	15.7	2395 (12.6)	1925 (10.3)	7.2
Southwestern	827 (9.5)	927 (11.6)	6.8	2292 (12.1)	2559 (13.7)	4.9
Southeastern	1974 (22.7)	2142 (26.9)	9.6	4417 (23.3)	5415 (29.1)	13.2

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin-receptor blocker; ASD = absolute standardized difference; CCB = calcium-channel blocker; COPD = chronic obstructive pulmonary disease; EAST-AFNET 4 = Early Treatment of Atrial Fibrillation for Stroke Prevention Trial; NOAC = non–vitamin K antagonist oral anticoagulant.

* Values are numbers (percentages) unless otherwise specified.

† Modified HAS-BLED = hypertension, 1 point; >65 years old, 1 point; stroke history, 1 point; bleeding history or predisposition, 1 point; liable international normalized ratio, not assessed; ethanol or drug abuse, 1 point; and drug predisposing to bleeding, 1 point.

‡ Defined as a prescription fill of >90 d within 180 d after the first prescription for rhythm or rate control drugs or an ablation procedure for AF.

VASc scores (median, 4 vs. 1); had more comorbid conditions, including heart failure, hypertension, diabetes, vascular disease, and stroke; and more frequently used oral anticoagulants at the time of treatment initiation (**Supplement Table 6**, available at Annals.org). The most commonly used rhythm control strategies were the class Ic drug propafenone (36.4%) in ineligible patients and the class III drug amiodarone (38.2%) in eligible patients (**Figure 2**). In the ineligible and eligible groups, ablation was an initial rhythm control strategy in 1.6% and 0.9% of patients, respectively, and was done during follow-up in 12.4% and 4.9% of patients, respectively (**Figure 2**).

Low-Risk Patients Ineligible for EAST-AFNET 4

Among those who did not meet the inclusion criteria, rhythm and rate control treatments were initiated in 8684 and 7975 patients, respectively. Patients using rhythm control tended to be male, live in a metropolitan area, have a longer AF duration, and have a higher income than patients using rate control (**Table 1**). After overlap weighting, sociodemographic and clinical characteristics were well balanced between the groups (**Supplement Table 7**, available at Annals.org).

Patients were followed for a median of 3.0 years (IQR, 1.9 to 4.1 years) among those using rhythm control and 3.2 years (IQR, 2.0 to 4.4 years) among those using rate control. Early rhythm control was associated with a reduction in the primary composite outcome compared with early rate control (weighted incidence rate, 1.60 vs. 2.00 events per 100 person-years; HR, 0.81 [95% CI, 0.66 to 0.98]) (**Table 2** and **Figure 3**, *left*). There were trends toward lower risks for all individual components of the primary composite outcome in patients receiving rhythm control versus rate control (**Table 2** and **Supplement Figure 4**, available at Annals.org). The mean number of nights spent in the hospital per year was lower in the early rhythm control group than in the early rate control group (6.1 vs. 8.5 nights per year) (**Table 2**).

Risk for the composite safety outcome did not differ between the early rhythm control and rate control groups (3.59 vs. 3.42 events per 100 person-years; HR, 1.05 [CI, 0.92 to 1.20]) (**Table 3**).

Patients Eligible for EAST-AFNET 4

Among patients eligible for EAST-AFNET 4, rhythm and rate control treatments were initiated in 18 944 and 18 613 patients, respectively. Patients receiving rhythm control were likely to be younger and have a longer AF duration, higher income, and higher comorbidity index (**Table 1**). After weighting, all variables were balanced between the groups (**Supplement Table 7**).

Patients were followed for a median of 2.8 years (IQR, 1.7 to 4.0 years) among those using rhythm control and a median of 2.7 years (IQR, 1.7 to 3.9 years) among those using rate control. Consistent with the observations in the ineligible patients, early rhythm control in the eligible patients was associated with lower risk for the primary composite outcome compared with rate control (weighted incidence rate, 6.57 vs. 7.68 events per 100 person-years; HR, 0.86 [CI, 0.81 to 0.92]) (**Table 2** and **Figure 3**, *right*). Early rhythm control was associated with lower risks for all individual components of the primary composite outcome (**Table 2** and **Supplement Figure 4**). The mean number of nights spent in the hospital per year was lower in the early rhythm control group than in the early rate control group (25.7 vs. 28.5 nights per year) (**Table 2**).

Table 2. Efficacy Outcomes in Patients Undergoing Rhythm or Rate Control

Outcome	Rhythm Control			Rate Control			Absolute Rate Difference per 100 Person-Years (95% CI)*	Weighted HR (95% CI)†
	Events, *n*	Person-Years	Event Rate*	Events, *n*	Person-Years	Event Rate*		
Did not meet inclusion criteria for EAST-AFNET 4								
	n = 8684			*n* = 7975				
Primary composite outcome	281	21 978	1.60	476	20 970	2.00	−0.40 (−0.87 to 0.07)	0.81 (0.66 to 0.98)
Components of primary outcome								
Cardiovascular death	35	22 333	0.25	90	21 602	0.35	−0.10 (−0.29 to 0.09)	0.73 (0.45 to 1.18)
Ischemic stroke	136	22 137	0.61	177	21 362	0.79	−0.18 (−0.48 to 0.11)	0.77 (0.58 to 1.04)
Hospitalization for heart failure	101	22 205	0.70	2221	21 244	0.89	−0.19 (−0.50 to 0.12)	0.80 (0.59 to 1.07)
Acute myocardial infarction	24	22 300	0.12	44	21 535	0.18	−0.06 (−0.19 to 0.08)	0.68 (0.34 to 1.36)
Mean nights spent in hospital per year (SD)		6.1 (25.6)			8.5 (32.8)		−2.4 (−3.3 to −1.5)‡	-
Eligible for EAST-AFNET 4								
	n = 18 944			*n* = 18 613				
Primary composite outcome	2482	41 641	6.57	3344	40 808	7.68	−1.11 (−1.73 to −0.48)	0.86 (0.81 to 0.92)
Components of primary outcome								
Cardiovascular death	691	44 473	1.80	1046	44 590	2.07	−0.27 (−0.59 to 0.04)	0.88 (0.78 to 0.99)
Ischemic stroke	1000	43 147	2.47	1357	42 826	3.11	−0.64 (−1.03 to −0.26)	0.80 (0.73 to 0.88)
Hospitalization for heart failure	1112	42 968	2.92	1573	42 527	3.33	−0.41 (−0.82 to −0.00)	0.89 (0.81 to 0.98)
Acute myocardial infarction	159	44 266	0.33	176	44 367	0.47	−0.14 (-0.28 to −0.00)	0.71 (0.55 to 0.92)
Mean nights spent in hospital per year (SD)		25.7 (67.4)			28.5 (70.2)		−2.8 (−4.2 to −1.4)‡	-

EAST-AFNET 4 = Early Treatment of Atrial Fibrillation for Stroke Prevention Trial; HR = hazard ratio.
* Weighted incidence rate (per 100 person-years) comparing patients using rhythm vs. rate control after overlap weighting was applied.
† The competing risk regression model included only the treatment variable because all of the clinical variables listed in Table 1 had been well balanced by weighting.
‡ $P < 0.001$ for the difference between the treatment groups estimated using a 2-sample weighted *t* test.

Risk for the composite safety outcome did not differ between the rhythm control and rate control groups (9.14 vs. 9.22 events per 100 person-years; HR, 0.99 [CI, 0.94 to 1.05]) (**Table 3**).

Sensitivity Analyses

Subgroup analyses showed no interactions between the protective associations of early rhythm control with the primary composite outcome and sex, age, oral anticoagulation, level of care in which the treatment was initiated, or CHA_2DS_2-VASc score in the ineligible and eligible groups (**Supplement Figure 5**, available at Annals.org).

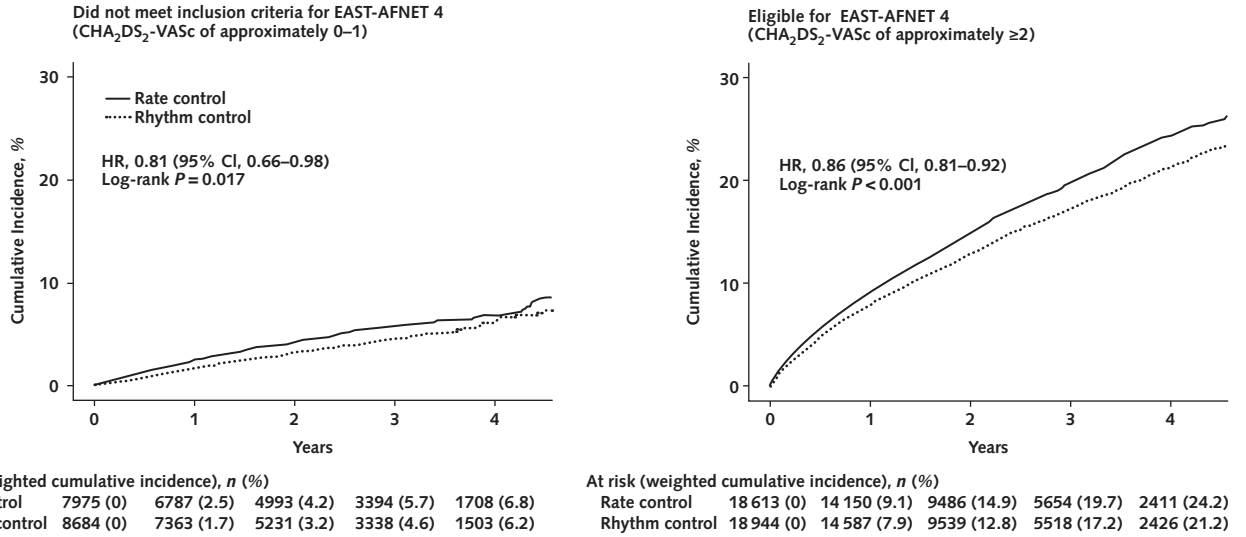
Among patients who did not meet the inclusion criteria, 885 (11.1%) switched from rate control to rhythm control therapy, whereas 3938 (45.3%) switched from rhythm control to rate control therapy. Among the patients eligible for the EAST-AFNET 4 study, 1379 (7.4%) switched from rate control to rhythm control, whereas 8714 (46.0%) switched from rhythm control to rate control (**Supplement Table 8**, available at Annals.org). The results from the competing risk regression, which included all of the variables used in propensity score calculation as covariates (**Supplement Table 9**, available at Annals.org), and the time-varying regression analyses (**Supplement Table 10**, available at Annals.org) were consistent with the main findings. Using 1:1 propensity score matching (**Supplement Table 11**, available at Annals.org) and using a 30-day enrollment period instead of the 180 days after initiation of treatment (**Supplement Table 12**, available at Annals.org) generated results similar to the main findings. In the analyses of 30 falsification end points, the 95% CIs of the associations between rhythm control and each end point contained 1 for 30 end points (100%) in the ineligible group and 30 (100%) in the eligible group (**Supplement Table 13**, available at Annals.org).

DISCUSSION

In the present study, almost 70% of patients recently diagnosed with AF were eligible for EAST-AFNET 4. The protective associations between early rhythm control and cardiovascular outcomes were similar for the eligible patients (risk reduction: absolute, 1.1 events per 100 person-years; relative, 14%) and the low-risk patients who did not meet the inclusion criteria (risk reduction: absolute, 0.4 events per 100 person-years; relative, 19%). For safety outcomes, we found no differences between the early rhythm control and rate control strategies regardless of trial eligibility. Our findings support the early initiation of rhythm control treatment in all patients recently diagnosed with AF independent of their estimated stroke risk.

Current guidelines recommend rhythm control therapy for symptom relief and quality-of-life improvement (2, 16). There have been no indications for rhythm control use to prevent adverse cardiovascular events or associated death on the basis of previous trials showing no effects of rhythm control on cardiovascular outcomes (6–8). The recent EAST-AFNET 4 showed that rhythm control therapy was associated with lower risk for adverse cardiovascular outcomes compared with usual care among patients with recently diagnosed AF and cardiovascular conditions in whom the median CHA_2DS_2-VASc score was 3 (9). In the ATHENA (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy

Figure 3. Weighted cumulative incidence curves of the primary composite outcome in patients recently (within 1 y) diagnosed with AF who did not meet the EAST-AFNET 4 inclusion criteria (*left*) and who would be eligible for the trial (*right*).



At risk (weighted cumulative incidence), *n* (%)

Rate control	7975 (0)	6787 (2.5)	4993 (4.2)	3394 (5.7)	1708 (6.8)
Rhythm control	8684 (0)	7363 (1.7)	5231 (3.2)	3338 (4.6)	1503 (6.2)

At risk (weighted cumulative incidence), *n* (%)

Rate control	18 613 (0)	14 150 (9.1)	9486 (14.9)	5654 (19.7)	2411 (24.2)
Rhythm control	18 944 (0)	14 587 (7.9)	9539 (12.8)	5518 (17.2)	2426 (21.2)

AF = atrial fibrillation; EAST-AFNET 4 = Early Treatment of Atrial Fibrillation for Stroke Prevention Trial; HR = hazard ratio.

of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter) trial, the antiarrhythmic drug dronedarone compared with placebo reduced the composite outcome of death or cardiovascular hospitalization in patients with AF who were aged 75 years or older or had additional risk factors (17). The positive effect was also noted in the CASTLE-AF (Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation) trial, which compared catheter ablation and medical treatment in patients with AF and systolic heart failure (18). Although the findings of ATHENA, CASTLE-AF, and EAST-AFNET 4 suggest a protective effect of rhythm control on cardiovascular complications, these results were obtained among patients with stroke risk factors. The present study shows that the effect of early rhythm control in improving outcomes was prominent in low-risk patients and supports initiatives for active consideration of rhythm control among all patients recently diagnosed with AF in clinical practice.

The point estimate for the association of early rhythm control with lower risk for the primary composite outcome among patients eligible for the trial was less prominent in this study (HR, 0.86) than in EAST-AFNET 4 (HR, 0.79), which might be explained by a shorter follow-up period (median, 2.7 vs. 5.1 years, respectively). The overall anticoagulation rate was substantially lower in the eligible patients in this study (43.5%) than in EAST-AFNET 4 participants (91.2%), whereas the median CHA_2DS_2-VASc score was higher in this study (4 vs. 3). These results might reflect the underuse of anticoagulation among patients with AF in routine clinical practice. In a recent study enrolling only patients who were receiving anticoagulation and were eligible for EAST-AFNET 4 in clinical practice, early rhythm control was associated with reduced risk for the primary composite outcome, with an HR of 0.81. This is closer to the HR found in EAST-AFNET 4 (19), suggesting that the benefit of early rhythm control might be attenuated by suboptimal use of anticoagulants in this study. Among the low-risk patients who did not meet the inclusion criteria for EAST-AFNET 4 in this study, the beneficial association of early rhythm control was more prominent than expected, although the follow-up duration was insufficient (median, 3.1 years). As expected, the overall event rate in the population (median CHA_2DS2-VASc score, 1) was approximately one fourth of that in the eligible population (median CHA_2DS2-VASc score, 4), suggesting the need for a large sample to verify the results in this low-risk population and showing the robustness of the association observed in such an underpowered setting. The more frequent use of catheter ablation in low-risk patients could affect the favorable outcomes of rhythm control. Although recent studies have demonstrated the safety of modern rhythm control therapy, including catheter ablation, safety concerns remain regarding rhythm control in both younger, low-risk patients and elderly, high-risk patients (5, 20–22). The present study discovered no significant differences in safety outcomes between rhythm control and rate control in either group, suggesting no need for tradeoffs sacrificing safety for better cardiovascular outcomes. The incidences of all-cause mortality were also lower in the rhythm control than rate control groups for both ineligible and eligible patients. Although the proportions of digoxin use were well balanced between the rhythm and rate control groups after overlap weighting and although the effect of digoxin on mortality is controversial, the higher use of digoxin in the rate control group might have affected the mortality rate (23–25).

Table 3. Safety Outcomes in Patients Undergoing Rhythm or Rate Control*

Outcome	Did Not Meet Inclusion Criteria for EAST-AFNET 4			Eligible for EAST-AFNET 4		
	Event Rate		Absolute Rate Difference per 100 Person-Years (95% CI)	Event Rate		Absolute Rate Difference per 100 Person-Years (95% CI)
	Rhythm Control (*n* = 8684)	Rate Control (*n* = 7975)		Rhythm Control (*n* = 18 944)	Rate Control (*n* = 18 613)	
Composite safety outcome	3.59	3.42	0.16 (−0.50 to 0.83)†	9.14	9.22	−0.07 (−0.78 to 0.63)‡
All-cause death	0.84	1.30	−0.46 (−0.82 to −0.10)	4.65	5.51	−0.86 (−1.37 to −0.35)
Intracranial bleeding	0.26	0.19	0.07 (−0.09 to 0.23)	0.60	0.69	−0.09 (−0.27 to 0.09)
Gastrointestinal bleeding	0.56	0.83	−0.27 (−0.56 to 0.03)	1.63	2.06	−0.44 (−0.75 to −0.13)
Serious adverse event related to rhythm control						
Cardiac tamponade	0.09	0.02	0.07 (−0.01 to 0.15)	0.10	0.05	0.05 (−0.01 to 0.11)
Syncope	1.27	0.96	0.31 (−0.06 to 0.68)	1.81	1.39	0.42 (0.13 to 0.71)
Sick sinus syndrome	0.46	0.13	0.33 (0.14 to 0.52)	0.96	0.33	0.63 (0.44 to 0.81)
Atrioventricular block	0.27	0.18	0.09 (−0.08 to 0.25)	0.37	0.23	0.14 (0.02 to 0.27)
Pacemaker implantation	0.13	0.04	0.09 (−0.01 to 0.19)	0.37	0.18	0.19 (0.07 to 0.31)
Sudden cardiac arrest	0.20	0.30	−0.10 (−0.27 to 0.08)	0.61	0.62	−0.01 (−0.19 to 0.17)

EAST-AFNET 4 = Early Treatment of Atrial Fibrillation for Stroke Prevention Trial.
* Outcomes are presented as weighted rates per 100 person-years after overlap weighting was applied.
† Risk for the composite safety outcome did not significantly differ according to treatment strategy, with a weighted hazard ratio of 1.05 (95% CI, 0.92 to 1.20).
‡ Risk for the composite safety outcome did not significantly differ according to treatment strategy, with a weighted hazard ratio of 0.99 (95% CI, 0.94 to 1.05).

The present study has several limitations. In this claims-based database, the burden of AF (rhythm status) was not evaluated. Thus, its role as a contributor to cardiovascular outcomes remains unknown. Because we defined AF diagnoses and ablation cases using only International Classification of Diseases, Tenth Revision, or claim codes, data on AF types or symptoms (paroxysmal vs. nonparoxysmal, symptomatic vs. asymptomatic) were not available. Because of the active comparator design of this study, asymptomatic patients with AF who did not require any treatment were excluded. Therefore, caution is needed in generalization of the results to asymptomatic patients. Willems and colleagues (26) recently found that the benefit of early rhythm control was consistent regardless of symptom status in the EAST-AFNET 4 participants. Our observational study findings cannot be used to establish causal relationships, and residual confounding may persist even after propensity score weighting or matching. We could not determine the exact reasons for the selection of rhythm control over rate control, which could have introduced bias. Moreover, unmeasured confounders (anticoagulation quality and lifestyle factors, such as obesity, alcohol intake, and physical activity) may have influenced the findings. Nonetheless, the results of the falsification analysis showed that the possibility of a systematic bias was low. We identified sufficient overlaps in propensity scores between the groups, which represents the existence of equipoise between the 2 treatment strategies (27). During follow-up, there were frequent crossovers between treatment strategies, especially from rhythm control to rate control. The magnitudes of protective associations observed in the time-varying analyses were more prominent than those in the main analyses, suggesting that the effect of early rhythm control on cardiovascular outcomes might not have been overestimated because of frequent crossovers. The proportions of patients treated with catheter ablation at baseline (within 180 days of the initiation of rhythm control) were low–1.6% of ineligible patients and 0.9% of eligible patients– although the proportions increased to 12.4% and 4.9%, respectively, at the end of follow-up. The low use of ablation as an initial therapy in our study compared with EAST-AFNET 4 might affect the generalizability of the results. Because of the new-user design, wherein prevalent drug users at the time of AF diagnosis were excluded, the proportion of treatment strategies selected in this study cannot fully reflect the preferences in real-world clinical practice.

In conclusion, approximately 70% of patients recently diagnosed with AF are eligible for EAST-AFNET 4 in routine clinical practice. The beneficial association between early rhythm control (vs. rate control) and cardiovascular outcomes was consistently observed in low-risk patients who did not meet the EAST-AFNET 4 eligibility criteria, as well as in the eligible patients.

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