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ORIGINAL RESEARCH

# Comparative Effectiveness of Early Rhythm Control Versus Rate Control for Cardiovascular Outcomes in Patients With Atrial Fibrillation

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**BACKGROUND:** Rhythm control is associated with better cardiovascular outcomes than usual care among patients with recently diagnosed atrial fibrillation (AF). This study investigated the effects of rhythm control compared with rate control on the incidence of stroke, heart failure, myocardial infarction, and cardiovascular death stratified by timing of treatment initiation.

**METHODS AND RESULTS:** We conducted a retrospective population-based cohort study including 22 635 patients with AF newly treated with rhythm control (antiarrhythmic drugs or ablation) or rate control in 2011 to 2015 from the Korean National Health Insurance Service database. Propensity overlap weighting was used. Compared with rate control, rhythm control initiated within 1 year of AF diagnosis decreased the risk of stroke. The point estimates for rhythm control initiated at selected time points after AF diagnosis are as follows: 6 months (hazard ratio [HR], 0.76; 95% CI, 0.66–0.87), 1 year (HR, 0.78; 95% CI, 0.66–0.93), and 5 years (HR, 1.00; 95% CI, 0.45–2.24). The initiation of rhythm control within 6 months of AF diagnosis reduced the risk of hospitalization for heart failure: 6 months (HR, 0.84; 95% CI, 0.74–0.95), 1 year (HR, 0.96; 95% CI, 0.82–1.13), and 5 years (HR, 2.88; 95% CI, 1.34–6.17). The risks of myocardial infarction and cardiovascular death did not differ between rhythm and rate control regardless of treatment timing.

**CONCLUSIONS:** Early initiation of rhythm control was associated with a lower risk of stroke and heart failure–related admission than rate control in patients with recently diagnosed AF. The effects were attenuated as initiating the rhythm control treatment later.

**Key Words:** atrial fibrillation ■ cardiovascular outcome ■ rate control ■ rhythm control



Atrial fibrillation (AF) increases the risk of mortality and morbidity caused by stroke and congestive heart failure (HF) and impairs quality of life.[1–3] Previous randomized trials comparing rhythm-control and rate-control strategies, including the landmark AFFIRM (Atrial Fibrillation Follow-up Investigation of Sinus Rhythm Management), have reported no significant differences between the treatment strategies with respect to mortality and stroke incidence.[4–6] Similarly, a meta-analysis of 5 randomized trials comparing the rhythm-control strategy with the rate-control strategy indicated no significant differences of the risk for all-cause mortality, although the results appeared to favor the rate-control strategy.[7]

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## CLINICAL PERSPECTIVE

### What Is New?

- In patients with atrial fibrillation and concomitant cardiovascular conditions, early initiation of rhythm control was associated with a lower risk of stroke and heart failure–related admission than rate control.

### What Are the Clinical Implications?

- The results call for shared decision-making regarding the benefits of rhythm-control therapy on cardiovascular outcomes in patients recently diagnosed with atrial fibrillation.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **AFFIRM** | Atrial Fibrillation Follow-up Investigation of Sinus Rhythm Management |
| **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 |
| **EAST-AFNET 4** | Early Treatment of AF for Stroke Prevention Trial |
| **NHIS** | National Health Insurance Service |
| **PALLAS** | Permanent Atrial Fibrillation Outcome Study |

By contrast, recent studies have revealed that rhythm control is associated with a lower risk of adverse cardiovascular outcomes than usual care among patients with recently (within 1 year) diagnosed AF.[8,9] EAST-AFNET 4 (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial) revealed that patients randomly assigned to receive early rhythm control had a low risk of death attributable to cardiovascular causes, stroke, and hospitalization for the worsening of HF or acute coronary syndrome, as well as a low risk of individual components of death attributable to cardiovascular causes and stroke.[8] Principally, a restored and maintained sinus rhythm with reduced AF burden is expected to reduce the risk of stroke, HF, and other cardiovascular outcomes and result in a good prognosis.[10,11] However, how early should we start rhythm control and which individual cardiovascular outcomes are improved by the early rhythm control are unclear. This study examined the comparative effectiveness of rhythm control versus rate control on cardiovascular outcomes stratified by the timing of treatment initiation.

## METHODS

This study is a retrospective analysis based on the national health claims database established by the National Health Insurance Service (NHIS) of Korea. All data and materials have been made publicly available at the NHIS of Korea. The data can be accessed on the National Health Insurance Data Sharing Service homepage of the NHIS (http://nhiss.nhis.or.kr). Applications to use the NHIS data will be reviewed by the inquiry committee of research support and, once approved, raw data will be provided to the authorized researcher for a fee at several permitted sites. A majority (97.1%) of the Korean population mandatorily subscribes to the NHIS, which is a single insurer managed by the Korean government, with the remaining 3% categorized as medical aid patients. As the database also includes information of the medical aid population, it can be considered to represent the entire Korean population. This study was approved by the institutional review board of the Yonsei University Health System (4-2016-0179). The requirement for informed consent was waived because personal identification information was removed after cohort generation, in accordance with strict confidentiality guidelines. The NHIS database includes information on drug prescriptions for the entire Korean population from January 1, 2002, which provides a minimum look-back period of 9.5 years before each individual's date of inclusion (the earliest date of inclusion was July 28, 2011).

### Cohort Design and Study Population

The details of the study protocol are presented in Table S1. We identified adults (age ≥18 years) with AF who were treated with rhythm- or rate-control strategies between July 28, 2011, and December 31, 2015, and who were aged >75 years, had a history of a transient ischemic attack or stroke, or met 2 of the following criteria: age >65 years, female sex, HF, hypertension, diabetes, previous myocardial infarction (MI), or chronic kidney disease, using a similar inclusion period and criteria as EAST-AFNET 4.[8] AF was defined according to the *International Classification of Diseases, Tenth Revision* (*ICD-10*), code I48. The diagnosis of AF has previously been validated in the NHIS database with a positive predictive value of 94.1%.[12] We used a new-user and intention-to-treat design for rhythm- or rate-control treatments. New

users were defined as those with no previous records of prescriptions or procedures of interest in the database. Intention to treat with rhythm control was defined as a prescription of a >90-day supply of any rhythm-control drugs in the 180-day period since the first prescription or performance of an ablation procedure for AF. Intention-to-treat with rate control was defined as a prescription of a >90-day supply of any rate-control drugs in the 180-day period since the first prescription, with no prescriptions of rhythm-control drugs and ablation within this period. Patients who were prescribed rhythm-control drugs for >90 days or who underwent ablation within the 180-day period since the initiation of rate-control drugs were classified into the intention-to-treat with rhythm control group (n=8350). Rhythm- and rate-control drugs and claim codes for ablation procedures are presented in Table S2. This study excluded patients without a prescription of a >90-day supply of warfarin or a direct oral anticoagulant within the 180-day period since the initiation of rhythm- or rate-control drugs or the performance of an ablation procedure for AF and those who died within 180 days of the first record of a prescription or procedure (Figure 1A).

## Outcome and Covariates

We investigated the individual components of the primary composite outcome of EAST-AFNET 4: ischemic stroke, hospitalization cause by HF, acute MI, and cardiovascular death. Detailed definitions of the outcomes are presented in Table S3. The study outcomes were followed up from 180 days after the first recorded prescription or procedure. Patients were followed up until the occurrence of study outcomes, death, or the end of the study period (December 31, 2016), whichever came earliest. Each clinical outcome was analyzed independently of the other without being censored.

We obtained information regarding selected baseline comorbid conditions for the look-back period from January 1, 2002, up to the start of therapy from inpatient and outpatient hospital diagnoses and pharmacy claims. The patients were considered to have comorbidities when the condition was a discharge

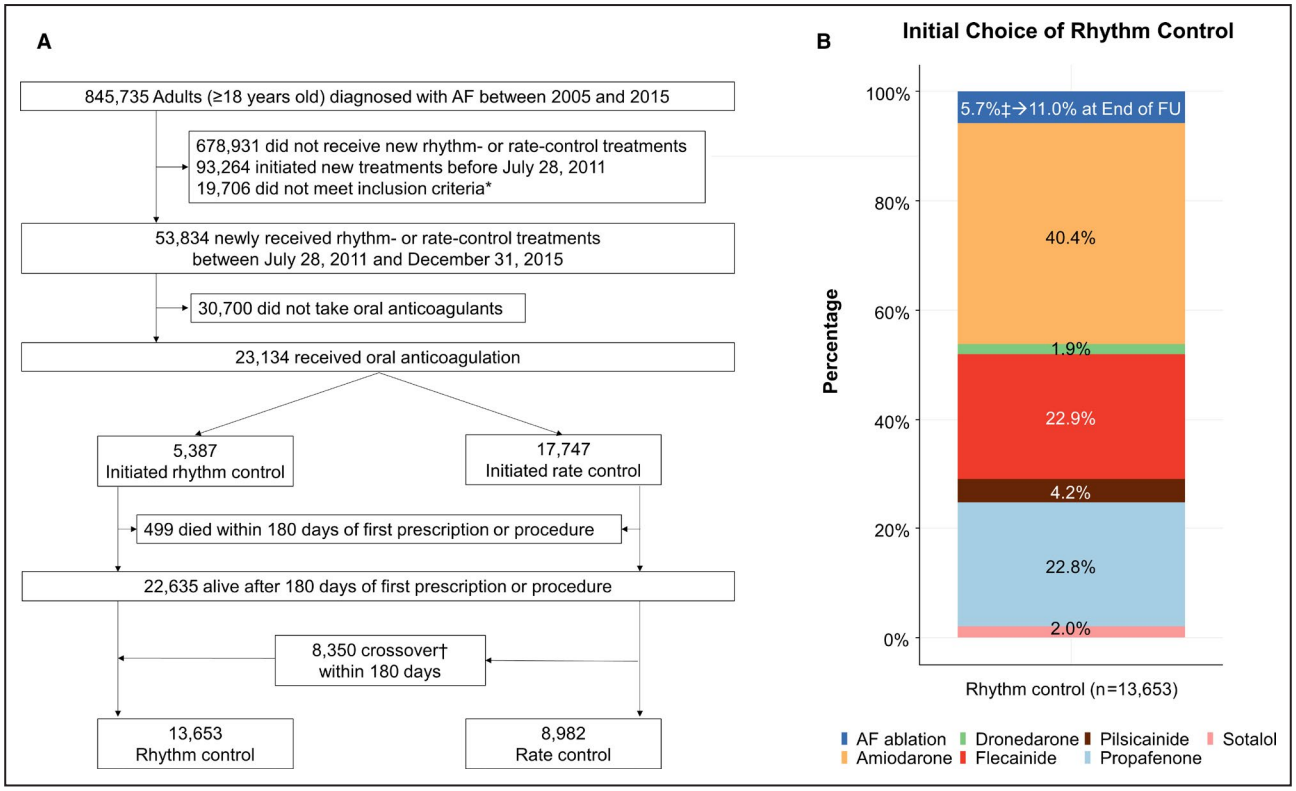


**Figure 1. Flowchart of the enrollment and analysis of the study population (A) and initial choice of rhythm-control treatments (B).**

*Older than 75 years, had a previous transient ischemic attack or stroke, or met 2 of the following criteria: age >65 years, female sex, heart failure, hypertension, diabetes, history of myocardial infarction, and chronic kidney disease. †Patients prescribed rhythm control drugs for >90 days or those who underwent ablation within the 180-day period since the initiation of rate-control drugs were classified as intention to treat with rhythm control. ‡Ablations performed within 180 days after the initial prescription of rhythm-control drugs were classified as initial choices for rhythm control. AF indicates atrial fibrillation.

diagnosis or was confirmed at least twice in an outpatient setting (Table S2). The Hospital Frailty Risk score was calculated retrospectively using 109 *ICD-10* diagnostic codes, which were found to be associated with frailty.[13] The baseline relative economic status was determined based on the health insurance premiums in the index year. Concurrent use of medication was verified by identifying NHIS database claims and defined as a prescription of a >90-day supply of the medication within the 180 days of the first record of a prescription or procedure for rhythm- or rate-control therapies.

## Statistical Analysis

Descriptive statistics were used to describe baseline characteristics. Overlap weighting based on a propensity score was used to assess the differences in baseline characteristics between the rhythm-control and rate-control groups. The propensity score, which represents the probability of receiving rhythm control, was estimated using logistic regression based on sociodemographic factors, time from AF diagnosis, year of therapy initiation, level of care at which the prescription was provided, clinical risk scores, medical history, and concurrent medication use (variables in Table). Continuous variables were modeled as cubic spline functions. The distribution of propensity scores before and after overlap weighting is shown in Figure S1. The overlap weight was calculated as 1 minus the propensity score for patients who received rhythm control, and as the propensity score for patients who received rate control, to obtain estimates representing the average treatment effects in the population with a minimized asymptotic variance of the treatment effect and desirable exact balance property.[14] The balance between the treatment populations was evaluated by standardized differences of all baseline covariates using a threshold of 0.1 to indicate imbalance. Competing risk regression by Fine and Gray was used to consider all-cause death as a competing event when estimating the relative hazards of clinical outcomes.[15] Cofactors that had not been balanced by weighting were included as covariates in the competing risk regression. The proportional hazards assumption was tested based on Schoenfeld residuals. To explore the treatment timing–dependent effect of rhythm control on the cardiovascular outcomes, Cox proportional hazards models were fit to the entire weighted study population using an interaction term for treatment timing after AF diagnosis (modeled as a natural spline) and treatment (rhythm-control or rate-control strategy). Standard errors were computed using 1000 bootstrap replicates. Two-sided *P* values of <0.05 were considered significant. Statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc) and R version 3.6.0 (The R Foundation, www.R-project.org).

## Sensitivity Analysis

First, we performed analyses in analogy to the on-treatment principle by censoring patients who switched to another treatment strategy or discontinued their treatment (censored at the time of switch or discontinuation). Second, one-to-one propensity score matching (without replacement with a calliper of 0.01) was used instead of overlap weighting. The balance of covariates after matching is shown in Table S4. Third, we performed stratified analysis based on whether the patients undergoing rhythm control were treated with catheter ablation or antiarrhythmic drugs, comparing each group with the patients undergoing rate control. Fourth, we conducted a separate propensity score overlap weighting analysis on restricted patients with access to anticoagulants covering at least 80% of the time at risk during follow-up. Fifth, we performed "falsification analysis" to measure systematic bias in this study by employing 45 prespecified falsification end points, with true hazard ratios (HRs) of 1. Detailed definitions of the falsification end points are presented in Table S5.

# RESULTS

## Patient Characteristics

In total, 9246 of 13 653 (67.7%) patients started receiving rhythm-control therapy within 1 year of AF diagnosis (early rhythm control). In contrast, 7077 of 8982 (78.8%) patients started receiving rate-control therapy within 1 year of AF diagnosis (early rate control) (Table). The most commonly used rhythm-control drug was the class III drug amiodarone (40.4%), followed by class Ic drugs (Figure 1B). Ablation was the initial rhythm-control strategy in 5.7% of patients and was eventually performed during follow-up in 11.0% of the patients in the rhythm-control group.

Patients in the rhythm-control group were more likely to have comorbidities such as hypertension, diabetes, vascular disease, and chronic kidney disease and less likely to have a history of HF-related admission and ischemic stroke than patients in the rate-control group. After overlap weighting, all baseline characteristics were similar between the 2 groups (Table).

## Stroke

During the mean follow-up of 2.3±1.3 years, 1419 patients experienced stroke: 715 (5.2%) in the rhythm-control group and 704 (7.8%) in the rate-control group. The rhythm-control strategy was associated with a reduction in stroke incidence compared with the rate-control strategy (2.80 versus 3.65 events per 100 person-years; HR, 0.77 [95% CI, 0.65–0.92]; *P*=0.004) (Figure 2). The rhythm-control strategy was consistently associated with a reduction in stroke incidence compared with the rate-control strategy in on-treatment analysis and after

**Table. Baseline Characteristics of Patients Receiving Rhythm- and Rate-Control Treatments Before and After Overlap Weighting**

| Variables | Before overlap weighting | | | After overlap weighting | | |
|---|---|---|---|---|---|---|
| | Rhythm control (n=13 653) | Rate control (n=8982) | ASD, % | Rhythm control (n=13 653) | Rate control (n=8982) | ASD, % |
| Sociodemographic | | | | | | |
| Age, y | 68 (60–75) | 72 (64–78) | 25.5 | 70 (62–76) | 71 (62–77) | <0.1 |
| <65 y | 4795 (35.1) | 2334 (26.0) | 19.9 | 29.7 | 29.7 | <0.1 |
| 65–74 y | 5279 (38.7) | 3160 (35.2) | 7.2 | 37.1 | 37.1 | <0.1 |
| ≥75 y | 3579 (26.2) | 3488 (38.8) | 27.2 | 33.1 | 33.1 | <0.1 |
| Men | 7364 (53.9) | 4836 (53.8) | 0.2 | 54.7 | 54.7 | <0.1 |
| AF duration, mo | 1.3 (0.0–31.5) | 0.0 (0.0–5.3) | 28.2 | 0.6 (0.0–13.6) | 0.1 (0.0–14.7) | <0.1 |
| Early AF (initiating treatment within 1 y after diagnosis) | 9246 (67.7) | 7077 (78.8) | 25.2 | 74.2 | 73.6 | 1.3 |
| Enrollment year | | | | | | |
| 2011 | 941 (6.9) | 581 (6.5) | 1.7 | 6.3 | 6.3 | <0.1 |
| 2012 | 2352 (17.2) | 1697 (18.9) | 4.3 | 18.1 | 18.1 | <0.1 |
| 2013 | 2859 (20.9) | 1974 (22.0) | 2.5 | 21.4 | 21.4 | <0.1 |
| 2014 | 3288 (24.1) | 2032 (22.6) | 3.5 | 23.1 | 23.1 | <0.1 |
| 2015 | 4213 (30.9) | 2698 (30.0) | 1.8 | 31.1 | 31.1 | <0.1 |
| High tertile of income | 6563 (48.1) | 3840 (42.8) | 10.7 | 44.8 | 44.8 | <0.1 |
| No. of OPD visits ≥12 per y | 11 812 (86.5) | 6968 (77.6) | 23.4 | 81.7 | 81.7 | <0.1 |
| Living in metropolitan areas | 6473 (47.4) | 3778 (42.1) | 10.8 | 44.7 | 44.7 | <0.1 |
| Level of care initiating treatment | | | | | | |
| Tertiary | 8570 (62.8) | 3633 (40.4) | 45.8 | 50.1 | 50.1 | <0.1 |
| Secondary | 4661 (34.1) | 4604 (51.3) | 35.1 | 44.6 | 44.6 | <0.1 |
| Primary | 422 (3.1) | 745 (8.3) | 22.6 | 5.3 | 5.3 | <0.1 |
| Risk scores | | | | | | |
| $CHA_2DS_2$-VASc | 4 (3–5) | 4 (3–5) | 4.3 | 4 (3–5) | 4 (3–5) | <0.1 |
| HAS-BLED* | 3 (2–3) | 3 (2–3) | 19.7 | 3 (2–3) | 3 (2–3) | <0.1 |
| Charlson comorbidity index | 4 (3–6) | 3 (2–5) | 33.9 | 4 (2–6) | 4 (2–6) | <0.1 |
| Hospital Frailty Risk Score | 2.8 (0.3–6.8) | 2.8 (0.1–7.0) | 2.4 | 3.0 (0.5–7.1) | 2.9 (0.3–7.1) | <0.1 |
| Medical history | | | | | | |
| HF | 7431 (54.4) | 4933 (54.9) | 1.0 | 54.9 | 54.9 | <0.1 |
| Previous hospitalization for HF | 1835 (13.4) | 1368 (15.2) | 5.1 | 14.5 | 14.5 | <0.1 |
| Hypertension | 11 923 (87.3) | 6094 (67.8) | 48.0 | 80.3 | 80.3 | <0.1 |
| Diabetes | 4336 (31.8) | 2310 (25.7) | 13.4 | 29.6 | 29.6 | <0.1 |
| Dyslipidemia | 11 990 (87.8) | 6934 (77.2) | 28.2 | 83.4 | 83.4 | <0.1 |
| Ischemic stroke | 4423 (32.4) | 3295 (36.7) | 9.0 | 35.8 | 35.8 | <0.1 |
| Transient ischemic attack | 1643 (12.0) | 785 (8.7) | 10.8 | 10.4 | 10.4 | <0.1 |
| Hemorrhagic stroke | 387 (2.8) | 249 (2.8) | 0.4 | 2.9 | 2.9 | <0.1 |
| MI | 1510 (11.1) | 605 (6.7) | 15.2 | 8.6 | 8.6 | <0.1 |
| Peripheral arterial disease | 2363 (17.3) | 1076 (12.0) | 15.1 | 14.6 | 14.6 | <0.1 |

(*Continued*)

**Table. Continued**

| Variables | Before overlap weighting | | | After overlap weighting | | |
|---|---|---|---|---|---|---|
| | Rhythm control (n=13 653) | Rate control (n=8982) | ASD, % | Rhythm control (n=13 653) | Rate control (n=8982) | ASD, % |
| Valvular heart disease | 1568 (11.5) | 1047 (11.7) | 0.5 | 11.5 | 11.5 | <0.1 |
| Chronic kidney disease | 1113 (8.2) | 428 (4.8) | 13.8 | 6.3 | 6.3 | <0.1 |
| Proteinuria | 1041 (7.6) | 613 (6.8) | 3.1 | 7.5 | 7.5 | <0.1 |
| Hyperthyroidism | 2074 (15.2) | 751 (8.4) | 21.3 | 10.8 | 10.8 | <0.1 |
| Hypothyroidism | 2177 (15.9) | 905 (10.1) | 17.5 | 12.4 | 12.4 | <0.1 |
| Malignancy | 3467 (25.4) | 2067 (23.0) | 5.6 | 24.7 | 24.7 | <0.1 |
| Chronic obstructive pulmonary disease | 4471 (32.7) | 2776 (30.9) | 4.0 | 32.3 | 32.3 | <0.1 |
| Chronic liver disease | 6330 (46.4) | 3388 (37.7) | 17.6 | 41.9 | 41.9 | <0.1 |
| Hypertrophic cardiomyopathy | 311 (2.3) | 94 (1.0) | 9.6 | 1.5 | 1.5 | <0.1 |
| Osteoporosis | 4930 (36.1) | 3154 (35.1) | 2.1 | 35.6 | 35.6 | <0.1 |
| Sleep apnea | 99 (0.7) | 34 (0.4) | 4.7 | 0.5 | 0.5 | <0.1 |
| Concurrent medication | | | | | | |
| Oral anticoagulant | 13 653 (100.0) | 8982 (100.0) | <0.1 | 100.0 | 100.0 | <0.1 |
| Warfarin | 10 950 (80.2) | 7525 (83.8) | 9.3 | 82.4 | 82.4 | <0.1 |
| Direct oral anticoagulant | 3464 (25.4) | 1955 (21.8) | 8.5 | 23.3 | 23.3 | <0.1 |
| β-Blocker | 6524 (47.8) | 6481 (72.2) | 51.4 | 69.2 | 69.2 | <0.1 |
| Nondihydropyridine CCB | 1759 (12.9) | 1377 (15.3) | 7.0 | 16.3 | 16.3 | <0.1 |
| Digoxin | 1106 (8.1) | 2927 (32.6) | 63.9 | 18.3 | 18.3 | <0.1 |
| Aspirin | 3015 (22.1) | 1662 (18.5) | 8.9 | 20.3 | 20.3 | <0.1 |
| $P2Y_{12}$ inhibitor | 1279 (9.4) | 759 (8.5) | 3.2 | 9.3 | 9.3 | <0.1 |
| Statin | 6213 (45.5) | 3952 (44.0) | 3.0 | 46.0 | 46.0 | <0.1 |
| Dihydropyridine CCB | 2897 (21.2) | 1170 (13.0) | 21.9 | 16.4 | 16.4 | <0.1 |
| ACEI/ARB | 7329 (53.7) | 4767 (53.1) | 1.2 | 53.3 | 53.3 | <0.1 |
| Loop/thiazide diuretics | 5536 (40.5) | 4715 (52.5) | 24.1 | 46.8 | 46.8 | <0.1 |
| $K^+$-sparing diuretics | 1970 (14.4) | 2105 (23.4) | 23.1 | 19.0 | 19.0 | <0.1 |
| α-Blocker | 290 (2.1) | 169 (1.9) | 1.7 | 1.9 | 1.9 | <0.1 |

Values are presented as median (interquartile range) or number (percentage) unless otherwise indicated. ACEI indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; ASD, absolute standardized difference; CCB, calcium channel blocker; HF, heart failure; MI, myocardial infarction; and OPD, outpatient department.

*A liable international normalized ratio was not assessed.



propensity score matching (Figure 2). The weighted cumulative incidence curves showed that the cumulative incidence of stroke was significantly lower in the rhythm-control group than in the rate-control group (log-rank $P<0.001$) (Figure 3A).

Cox proportional hazard models using an interaction term showed that compared with rate control, rhythm control initiated within 16 months after AF diagnosis decreased the risk of ischemic stroke. No difference in the risk of stroke was found between the rhythm- and rate-control strategies initiated after the 16 months of AF diagnosis (Figure 4A). Compared with rate control, rhythm control showed the following point estimates at selected time points after AF diagnosis: 6 months (HR, 0.76; 95% CI, 0.66–0.87), 1 year (HR, 0.78; 95% CI, 0.66–0.93), and 5 years (HR, 1.00; 95% CI, 0.45–2.24) (Figures 4A and 5). The benefit of early rhythm control for stroke risk was consistently observed in on-treatment analysis and after propensity score matching (Figure 5 and Figure S2A).

| Patient group | Rhythm control | | | Rate control | | | Absolute rate difference per 100 person-years (95% CI) | Hazard ratio (95% CI) | Favors rhythm control | Favors rate control | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. events | Person -years | Event rate | No. events | Person -years | Event rate | | | | | |
| **Propensity overlap weighting*** | | n=13653 | | | n=8982 | | | | | | |
| ***Intention to treat*** | | | | | | | | | | | |
| Ischemic stroke | 715 | 30228 | 2.80 | 704 | 19379 | 3.65 | -0.85 (-1.41 to -0.29) | 0.77 (0.65–0.92) | | | 0.004 |
| Hospitalization for heart failure | 921 | 29956 | 3.62 | 856 | 19098 | 4.20 | -0.57 (-1.19 to 0.05) | 0.84 (0.75–0.94) | | | 0.002 |
| Acute myocardial infarction | 78 | 31068 | 0.23 | 64 | 20172 | 0.37 | -0.14 (-0.31 to 0.03) | 0.62 (0.35–1.11) | | | 0.107 |
| Cardiovascular death | 523 | 31149 | 2.22 | 532 | 20253 | 2.44 | -0.21 (-0.68 to 0.56) | 0.92 (0.75–1.12) | | | 0.405 |
| **Propensity overlap weighting*** | | n=13653 | | | n=8982 | | | | | | |
| ***On treatment*** | | | | | | | | | | | |
| Ischemic stroke | 477 | 21333 | 2.71 | 604 | 15868 | 3.87 | -1.16 (-1.81 to -0.50) | 0.69 (0.56–0.85) | | | <0.001 |
| Hospitalisation for heart failure | 644 | 21169 | 0.66 | 745 | 15619 | 4.47 | -0.80 (-1.54 to -0.01) | 0.81 (0.67–0.97) | | | 0.023 |
| Acute myocardial infarction | 47 | 21746 | 0.23 | 59 | 16362 | 0.42 | -0.19 (-0.39 to 0.01) | 0.54 (0.27–1.05) | | | 0.069 |
| Cardiovascular death | 179 | 21788 | 1.14 | 199 | 16418 | 1.09 | 0.05 (-0.33 to 0.43) | 1.04 (0.74–1.46) | | | 0.824 |
| **Propensity score matching** | | n=5183 | | | n=5183 | | | | | | |
| ***Intention to treat*** | | | | | | | | | | | |
| Ischemic stroke | 302 | 11476 | 2.63 | 380 | 11236 | 3.38 | -0.75 (-1.20 to -0.30) | 0.78 (0.67–0.90) | | | 0.001 |
| Hospitalization for heart failure | 393 | 11399 | 3.45 | 449 | 11112 | 4.04 | -0.59 (-1.10 to -0.09) | 0.84 (0.74–0.97) | | | 0.014 |
| Acute myocardial infarction | 24 | 11856 | 0.20 | 42 | 11644 | 0.36 | -0.16 (-0.29 to -0.02) | 0.57 (0.34–0.94) | | | 0.027 |
| Cardiovascular death | 232 | 11878 | 1.95 | 273 | 11700 | 2.33 | -0.38 (-0.75 to -0.01) | 0.91 (0.77–1.08) | | | 0.270 |

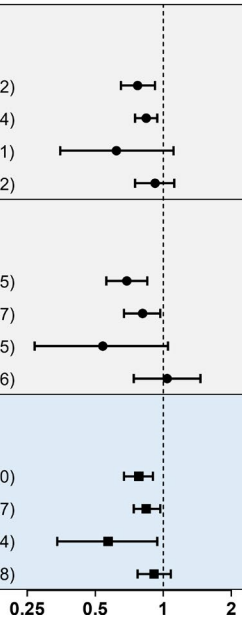


**Figure 2. Cardiovascular outcomes in patients receiving rhythm- and rate-control treatments.**
Event rates are per 100 person-years. *Incidences and hazard ratios are overlap weighted.

## HF-Related Hospitalization

After overlap weighting, 608 (2.7%) patients were found to have been hospitalized owing to HF during follow-up: 285 (1.3%) in the rhythm-control group and 323 (1.4%) in the rate-control group. The rhythm-control strategy was associated with a reduction in HF-related hospitalization incidence compared with the rate-control strategy (3.62 versus 4.20 events per 100 person-years; HR, 0.84 [95% CI, 0.75–0.94]; *P*=0.002) (Figure 2). This finding was consistently observed in on-treatment analysis and after propensity score matching (Figure 2). The weighted cumulative incidence curves showed that the cumulative incidence of HF-related hospitalization was significantly lower in the rhythm-control group than in the rate-control group (log-rank *P*=0.009) (Figure 3B).

Cox proportional hazard models using an interaction term showed that rhythm control initiated within 7 months of AF diagnosis decreased the incidence of HF-related hospitalization compared with rate control (Figure 4B). Rhythm control showed the following point estimates at selected time points after AF diagnosis: 6 months (HR, 0.84; 95% CI, 0.74–0.95), 1 year (HR, 0.96; 95% CI, 0.82–1.13), and 5 years (HR, 2.88; 95% CI, 1.34–6.17) (Figures 4B and 5). The benefit of initiating rhythm control within 6 months of AF diagnosis was consistently observed in on-treatment analysis and after propensity score matching (Figure 5 and Figure S2B).

## MI and Cardiovascular Death

In the overall weighted patients, rhythm control was not associated with a reduced risk of acute MI or cardiovascular death (Figure 2). Rhythm control initiated within 3 months of AF diagnosis was associated with a reduced risk of acute MI, with an HR of 0.59 (95% CI, 0.37–0.94) at 1 month after AF diagnosis (Figures 5 and 6A); however, the benefit of early rhythm control was not consistently observed in on-treatment analysis and propensity score–matched analysis (Figure 5). Early rhythm control did not reduce the incidence of cardiovascular death compared with early rate control (Figures 5 and 6B).

## Sensitivity Analysis

Overall, the beneficial association of rhythm control with stroke and HF-related hospitalization compared with rate control was more prominent for patients undergoing catheter ablation than for patients treated with antiarrhythmic drugs (Table S6). Regardless of the initial choice of rhythm-control treatments (catheter ablation or antiarrhythmic drugs), we consistently observed trends toward lower risks of outcomes for rhythm control initiated earlier (Figure S3). Enrolling only patients taking oral anticoagulants, at least 80% of their follow-up period (67.0% of the study population) showed consistent findings with the main results (Table S7 and Figure S4). In the analyses of 45

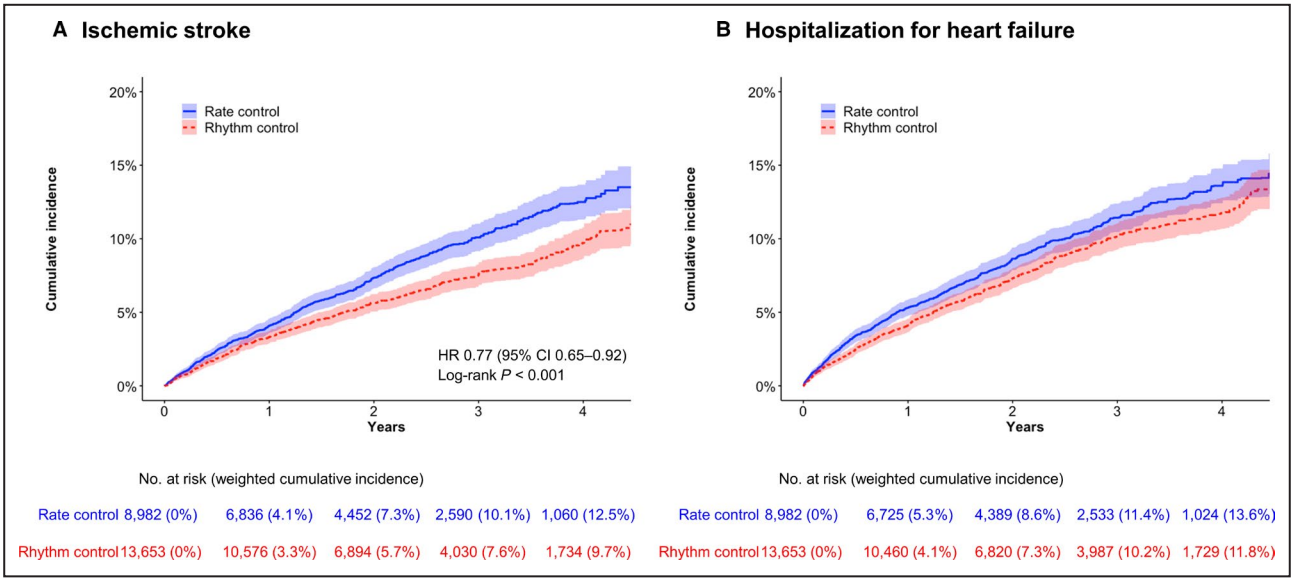


**Figure 3. Weighted cumulative incidence curves for ischemic stroke (A) and hospitalization for heart failure (B).**

falsification end points, the 95% CIs of the associations of rhythm-control with each end point covered 1 in 45 (100%) end points (Table S8).

## DISCUSSION

In this study, the initiation of rhythm control, rather than that of rate control, within 1 year of AF diagnosis was associated with a decreased risk of ischemic stroke. The initiation of rhythm control within 6 months of AF diagnosis was associated with a decreased risk of HF-related hospitalization. Furthermore, no differences were found in the incidence of acute MI and cardiovascular death between the 2 groups, regardless of the timing of treatment.

### Lower Risks of Stroke and HF Hospitalization by Early Rhythm Control

In EAST-AFNET 4, early rhythm control lowered the risk of stroke by 35% compared with usual care.[8]

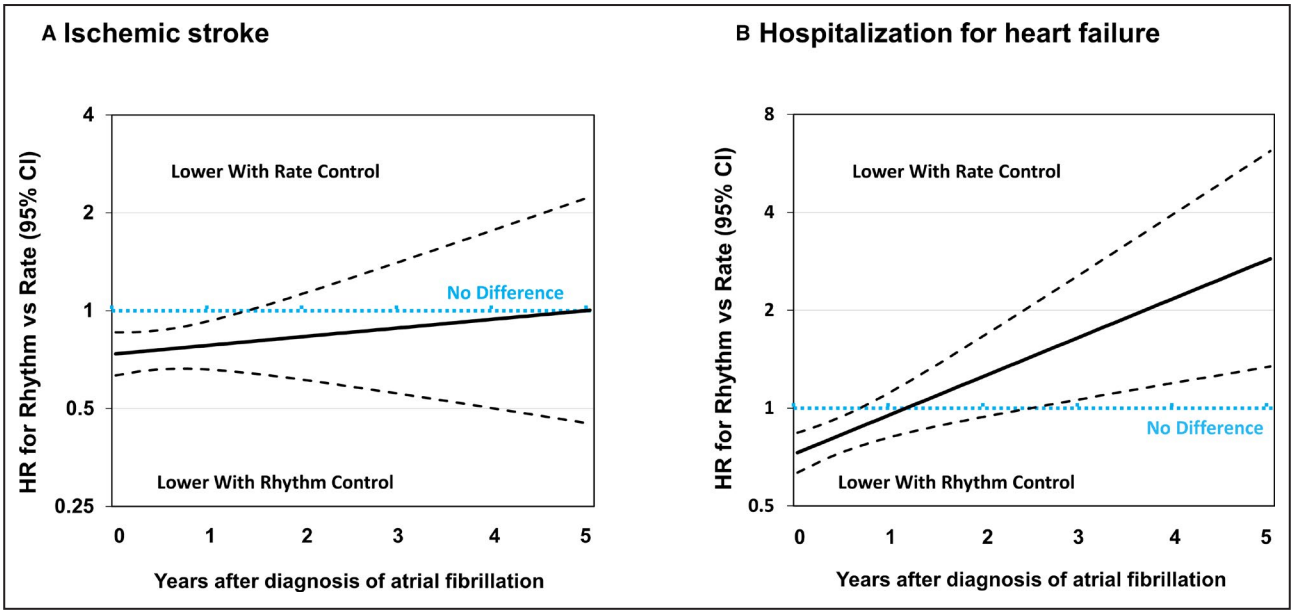


**Figure 4. Relationship between treatment timing and risk of ischemic stroke (A) and hospitalization owing to heart failure (B) for rhythm control or rate control.**

The *x*-axis shows the timing of treatment initiation since the first diagnosis of atrial fibrillation, and the *y*-axis, the hazard ratios (HRs) associated with rhythm control compared with rate control. The sky blue horizontal dotted lines indicate an HR of 1, which corresponds to an equal risk of outcomes in patients treated with rhythm and rate control. Dashed black lines show the 95% CI.

| Timing of initiation after AF diagnosis | Stroke | Hospitalization for heart failure | Acute myocardial infarction | Cardiovascular death |
|---|---|---|---|---|
| Propensity overlap weighting - Intention to treat (main analysis) | | | | |
| 6 months | 0.76 (0.66–0.87) | 0.84 (0.74–0.95) | 0.70 (0.45–1.09) | 0.92 (0.78–1.08) |
| 1 year | 0.78 (0.66–0.93) | 0.96 (0.82–1.13) | 0.87 (0.50–1.51) | 0.93 (0.76–1.13) |
| 2 years | 0.83 (0.61–1.14) | 1.26 (0.94–1.69) | 1.34 (0.49–3.61) | 0.94 (0.66–1.35) |
| 5 years | 1.00 (0.45–2.24) | 2.88 (1.34–6.17) | 4.83 (0.36–65.03) | 1.00 (0.39–2.58) |
| Propensity overlap weighting - On treatment (sensitivity analysis) | | | | |
| 6 months | 0.69 (0.59–0.81) | 0.76 (0.66-0.88) | 0.61 (0.29–1.28) | 1.03 (0.79–1.34) |
| 1 year | 0.71 (0.58–0.87) | 0.84 (0.70-1.01) | 0.71 (0.26–1.92) | 1.04 (0.75–1.45) |
| 2 years | 0.74 (0.51–1.07) | 1.00 (0.72-1.41) | 0.95 (0.15–6.08) | 1.07 (0.59–1.93) |
| 5 years | 0.85 (0.33–2.20) | 1.73 (0.71-4.21) | 2.30 (0.02–29.13) | 1.16 (0.24–5.45) |
| Propensity score matching - Intention to treat (sensitivity analysis) | | | | |
| 6 months | 0.78 (0.66–0.93) | 0.85 (0.73–0.99) | 0.92 (0.63–1.34) | 0.87 (0.71–1.06) |
| 1 year | 0.82 (0.65–1.02) | 0.98 (0.80–1.19) | 1.08 (0.65–1.79) | 0.90 (0.70–1.16) |
| 2 years | 0.88 (0.58–1.35) | 1.29 (0.89-1.86) | 1.49 (0.59–3.79) | 0.97 (0.60–1.55) |
| 5 years | 1.12 (0.37–3.37) | 2.95 (1.12–7.77) | 3.93 (0.35–43.69) | 1.19 (0.34–4.15) |

Favors rhythm control No difference Favors rate control

**Figure 5. Point estimates of rhythm control compared with rate control for cardiovascular outcomes according to timing of treatment initiation.**
AF indicates atrial fibrillation. Values are presented as hazard ratios (95% CIs).

Consistently, Kim et al[9] reported that the risk of stroke can be decreased 26% by early rhythm-control therapy rather than by rate-control therapy. In this study, rhythm control was associated with less frequent stroke events and a lower risk of stroke when initiated within 16 months of AF diagnosis. This result is in line with that of a post hoc analysis of 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), which demonstrated that dronedarone use was associated with a significant reduction in the risk of ischemic and hemorrhagic stroke.[16] In population-based observational cohort studies, rhythm control with antiarrhythmic drugs or catheter ablation was associated with lower rates of stroke/transient ischemic attack than rate-control therapy.[11,17]

In EAST-AFNET 4, early rhythm control showed a trend of reduction in the incidence of hospitalization for worsening of HF, without statistical significance.[8] Kim et al[9] assessed real-world data and reported that early rhythm control might be associated with a reduction in the risk of hospitalization for HF. In this study, rhythm control was associated with a lower risk of hospitalization for HF when initiated within 7 months of AF diagnosis. A large US cohort study reported that patients with AF who undergo ablation have a significantly lower risk of long-term HF than those who do not undergo ablation.[18] In a randomized controlled trial, catheter ablation for AF was associated with significantly lower rates of a composite end point of all-cause death and hospitalization for worsening HF in patients with HF and reduced ejection fraction.[19] The association between antiarrhythmic drug treatment and HF is not well known. However, dronedarone use was associated with a decreased incidence of hospitalization for HF in ATHENA, without statistical significance, owing to the small number of events.[16] In contrast, the results of PALLAS (Permanent Atrial Fibrillation Outcome Study) using dronedarone in addition to standard therapy indicated that dronedarone use increased the rates of HF, stroke, and death attributable to cardiovascular

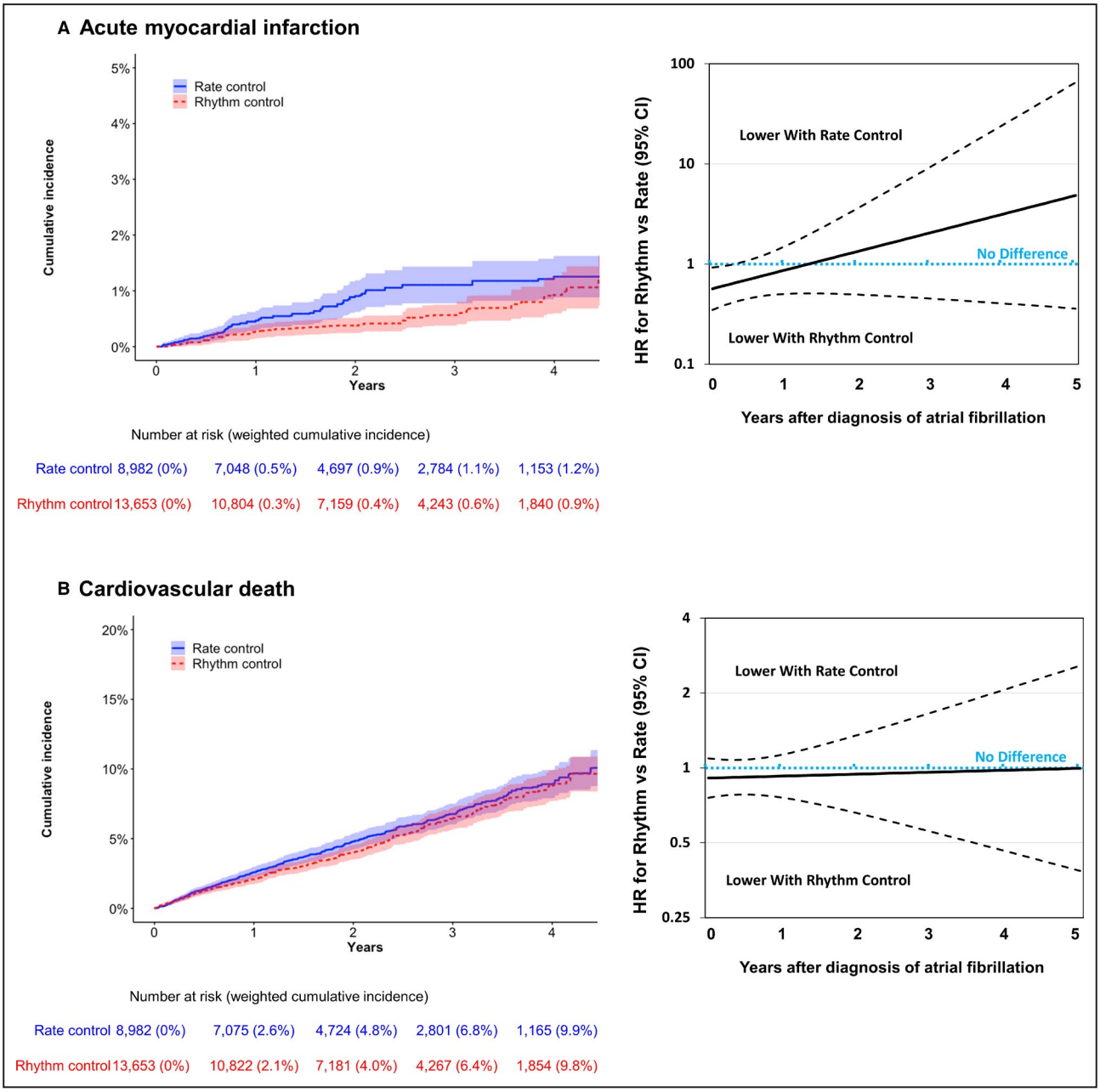


**Figure 6. Weighted cumulative incidence curves and relation between treatment timing and risk of acute myocardial infarction (A) and cardiovascular death (B).**
HR indicates hazard ratio.

causes in patients with permanent AF at risk for major vascular events.[20] Consistently, we observed trends in favor of the rate-control strategy when therapy initiation was delayed.

The association between early rhythm control and lower cardiovascular mortality in this study was less prominent than that in EAST-AFNET 4, which might be explained by a relatively shorter follow-up period (median, 2.5 versus 5.1 years in EAST-AFNET 4). Also, the low proportion of ablation as the initial choice for rhythm control (5.7%) in this study might contribute to the discrepant findings. The association between early rhythm control and acute MI has not been observed in previous studies.[8,9]

## Mechanism

Precise mechanisms by which early rhythm control confers benefits were not assessed in this clinical observational study; however, early rhythm control may be associated with an early impact on electrical and substrate remodeling.[21] In addition, patients receiving rhythm control may have had a more careful,

structured follow-up; however, in that case, we would have observed benefits in both the early and late rhythm-control subgroups. Contemporary rhythm-control treatments use antiarrhythmic drugs that are better tolerated and safer than those used (ie, class Ia agents) in trials comparing rate-control versus rhythm-control strategies 2 to 3 decades ago.[6] Yang et al[22] reported that no difference in survival, cardiovascular hospitalization incidence, or ischemic stroke incidence was found between patients with diagnosed AF within 6 months of study enrollment who were treated with rate control and rhythm control in AFFIRM. In addition, they concluded that the superiority of the rhythm-control strategy reported in recent AF trials may be more attributable to the refinement of AF therapies and less related to the timing of intervention. Although rhythm control included all major antiarrhythmic drugs and ablation in this study, both dronedarone and ablation are not popular choices for treatment of AF (dronedarone, 1.9%; ablation, 5.7%) (Figure 1B). These findings suggest that the favorable outcomes of rhythm control, which were only observed in patients with AF who started treatment shortly after diagnosis, could not be fully explained by the use of a promising drug or ablation, which may not have been available in previous trials, and might be associated with the timing of treatment.

## Study Limitations

The present study has several limitations. In this study, data from a claims-based database were used; hence, the burden of AF (rhythm status) was not evaluated. Thus, the role of AF burden, a contributor to outcomes, remains unknown. We defined AF diagnoses and ablation cases using only *ICD-10* or claim codes, and, therefore, data regarding AF type (paroxysmal versus nonparoxysmal) or symptoms (symptomatic versus asymptomatic) were not available. The findings from this observational study cannot be used to establish causal relationships, and residual confounding may persist even after propensity score weighting or matching. However, the results of the falsification analysis revealed that the presence of significant systematic bias was less likely. We were unable to determine the exact reasons for the selection of the rhythm-control strategy over the rate-control strategy, which may introduce potential bias, and the unmeasured confounders (quality of anticoagulation therapy and lifestyle factors such as obesity, alcohol intake, and physical activity) may have influenced the findings. Nonetheless, we identified sufficient overlap of propensity scores between the groups, which represents the existence of equipoise between the 2 therapies. The proportion of ablation as the initial choice for rhythm control was low. Ablation is permitted and reimbursed by national health insurance only in patients with documented AF after undergoing antiarrhythmic drug treatment for more than 6 weeks.[9] As first-line treatment, ablation is reimbursed only in those who cannot tolerate antiarrhythmic drugs owing to tachycardia-bradycardia syndrome or other conditions. Thus, the proportion of patients treated with catheter ablation at baseline (within 180 days after the initiation of rhythm control) is low (5.7%). The proportion was increased, however, to 11.0% at the end of follow-up, which was comparable to the 7% (as an initial choice) and 19.4% (at 2 years after randomization) in EAST-AFNET 4.[8] Because of the active-comparator design of this study, asymptomatic patients with AF who did not require therapy may have been excluded. In addition, because of the new-user design, according to which prevalent drug users at the time of AF diagnosis were excluded, the proportions of treatment strategies selected for patients with AF in this study may not fully reflect the preferences in real-world clinical practice. Last, this study enrolled only high-risk patients with a median $CHA_2DS_2$-VASc score of 4 using similar inclusion criteria as EAST-AFNET 4. Thus, further investigation is warranted to shed light on the effects of early rhythm control in patients with low risk.

# CONCLUSIONS

In this population-based sample of patients with AF, the initiation of early rhythm control was found to reduce the incidence of ischemic stroke and HF-related hospitalization in patients with AF compared with that of rate control. However, the effects of rhythm control were attenuated when initiating the treatments later.

## ARTICLE INFORMATION

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## Disclosures

Dr Lip has served as a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo; and as a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees have been directly or personally received. Dr Joung has served as a speaker for Bayer, BMS/Pfizer, Medtronic, and Daiichi-Sankyo; and received research funds from Medtronic and Abbott. No fees have been directly or personally received. The remaining authors have no disclosures to report.

## Supplementary Material

Tables S1–S8
Figures S1–S4

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# SUPPLEMENTAL MATERIAL

**Table S1. Summary of strategies for emulating target trial.**

| Components | Target trial (EAST-AFNET4) | This study |
|---|---|---|
| Inclusion period | July 28, 2011 – December 31, 2016 | July 28, 2011 – December 31, 2015 |
| Eligibility criteria | 1) Adults (≥18 years of age) who were older than 75 years of age, had had a previous transient ischemic attack or stroke, or met two of the following criteria: age greater than 65 years, female sex, heart failure, hypertension, diabetes mellitus, severe coronary artery disease, chronic kidney disease, and left ventricular hypertrophy<br>2) Early AF (diagnosed ≤12 months before enrolment) | 1) Selected adults (≥18 years of age) that received a rhythm-control or rate-control treatments and have no prior history of prescriptions and no records of ablation in the database who were older than 75 years of age, had a previous transient ischemic attack or stroke, or met two of the following criteria: age greater than 65 years, female sex, heart failure, hypertension, diabetes mellitus, myocardial infarction, and chronic kidney disease<br>2) Undergoing oral anticoagulation (>90 days of supply within 180 days after their first recorded prescription of rhythm- or rate-control medications or ablation procedure) |
| Exposed group | Rhythm control: AADs, AF ablation, cardioversion of persistent AF, to be initiated early after randomization | Rhythm control: a prescription of more than a 90-day supply of any rhythm-control drugs in the 180-day period since the first prescription or the performance of an ablation procedure for AF. |
| Unexposed group | Usual care: initially treated with rate-control therapy without rhythm-control therapy | Rate control: a prescription of more than a 90-day supply of any rate-control drugs in the 180-day period since the first prescription and with no prescription of rhythm-control drug and no ablation within this period.<br><br>Patients prescribed rhythm-control drugs for more than 90 days or who underwent ablation within the 180-day period since the initiation of rate-control drugs were classified as intention-to-treat with rhythm control. |
| Outcome | 1) A composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome<br>2) The number of nights spent in the hospital per year.<br>3) Each component of the primary composite outcome, rhythm, left ventricular function, quality of life, AF-related symptom | 1) Ischemic stroke<br>2) Hospitalization for heart failure<br>3) Acute myocardial infarction<br>4) Cardiovascular death |
| Follow-up | From randomization until the end of the trial, death, or withdrawal from the trial. | From 180 days after their first recorded prescription or procedure to avoid immortal time bias until the end of follow-up of the database (December 31, 2016) or death. |

**Table S2. Definitions and codes used for defining medical conditions, comorbidities, and drug treatments and procedures for atrial fibrillation.**

| | Definitions | Codes or conditions |
|---|---|---|
| **Medical conditions** | | |
| Atrial fibrillation | Defined from diagnosis* | I48 |
| Heart failure | Defined from diagnosis* | ICD-10: I11.0, I50, I97.1 |
| Heart failure admission history | Defined from principal or first secondary admission diagnoses of heart failure | ICD-10: I11.0, I50, I97.1 |
| Hypertension | Defined if fulfilling both diagnosis* and treatment within 90 days prior to the first recorded prescription or procedure for rhythm or rate control | ICD-10: I10, I11, I12, I13, I15<br>Treatment: prescription for at least one of all kinds of antihypertensive medication |
| Diabetes mellitus | Defined if fulfilling both diagnosis* and treatment within 90 days prior to the first recorded prescription or procedure for rhythm or rate control | ICD-10: E10, E11, E12, E13, E14<br>Treatment: prescription for at least one of all kinds of oral antidiabetics or insulin |
| Dyslipidemia | Defined from diagnosis* | ICD-10: E78 |
| Ischemic stroke | Defined from diagnosis* | ICD-10: I63, I64 |
| Transient ischemic attack | Defined from diagnosis* | ICD-10: G45 |
| Intracranial bleeding | Defined from diagnosis* | ICD-10: I60, I61, I62 |
| Myocardial infarction | Defined from diagnosis* | ICD-10: I21, I22, I25.2 |
| Peripheral arterial disease | Defined from diagnosis* | ICD-10: I70.0, I70.1, I70.2, I70.8, I70.9 |
| Valvular heart disease | Defined from diagnoses* mitral stenosis or claims for heart valve surgery | ICD-10: I05.0, I05.2, I34.2, Z95.2-4<br>Claim for valve replacement or valvuloplasty: O1781, O1782, O1783, O1791, O1792, O1793, O1797, O1794, O1795, O1796, O1798 |
| Chronic kidney disease | Defined from eGFR or diagnosis*<br>(if laboratory value was not available, diagnosis code was used) | eGFR <60mL/min per 1.73 $m^2$<br>ICD-10: N18, N19 |
| Proteinuria | Defined from laboratory data (if laboratory value was not available, diagnosis code* was used) | Urine dipstick proteinuria 1+ or higher (ICD-10: N06, N391, N392, R80) |
| Hyperthyroidism | Defined from diagnosis* | ICD-10: E05 |
| Hypothyroidism | Defined from diagnosis* | ICD-10: E03 |
| Malignancy | Defined from diagnoses* of cancer (non-benign) | ICD-10: C00-C97 |
| Chronic obstructive pulmonary disease | Defined if fulfilling both diagnosis* and treatment within 90 days prior to the first recorded prescription or procedure for rhythm or rate control | ICD-10: J42, J43(except J43.0), J44<br>Treatment: SABA, SAMA, LABA, LAMA, ICS, ICS+LABA, or methylxanthine (>1 months). |
| Chronic liver disease | Defined from diagnosis* of chronic liver disease, cirrhosis, and hepatitis | ICD-10: B18, K70, K71, K72, K73, K74, K76.1 |
| Hypertrophic cardiomyopathy | Defined from at least one records of either inpatient or | ICD-10: I42.1, I42.2 |

| | | |
|---|---|---|
| | outpatient diagnoses | |
| Osteoporosis | Defined from diagnosis* | ICD-10: M80, M81, M82 (except M82.0) |
| Sleep apnea | Defined from diagnosis* | ICD-10: G47.3 |
| **Drug treatment for atrial fibrillation (available in South Korea)** | | |
| Anti-arrhythmic drug | | |
| Class Ic | | flecainide, pilsicainide, propafenone |
| Class III | | amiodarone, dronedarone, sotalol |
| Rate control drugs | | |
| Beta-blocker | | atenolol, bisoprolol, carvedilol, metoprol, nebivolol, propranolol, labetalol |
| Calcium channel blocker | | diltiazem, verapamil |
| Cardiac glycosides | | digoxin |
| **Procedures for atrial fibrillation** | | |
| Catheter ablation for AF | Defined from admission diagnosis of AF plus claims for ablation procedures | ICD-10: I48<br>Claim codes: M6542 (Conventional Radiofrequency Ablation of Atrial fibrillation) or M6547 (Radiofrequency Ablation of Atrial fibrillation Through Intracardiac Electrophysiologic 3-Dimensional Mapping) |
| Cardioversion | Defined from diagnosis of AF plus claims for cardioversion | ICD-10: I48<br>Claim codes:M5880 |

*For greater accuracy, either one diagnosis during hospitalization or more than twice at outpatient clinics was requited for the diagnosis.

**Table S3. Definitions and codes used for study outcomes.**

| Outcomes | Definitions | Codes or conditions | PPV |
|---|---|---|---|
| Ischemic stroke | Defined from admission diagnosis with concomitant imaging studies of the brain or related death | ICD-10: I63, I64 | 90.6%* (2347/2591) |
| Hospitalization owing to heart failure | Defined from principal or first secondary admission diagnoses of heart failure | ICD-10: I11.0, I50, I97.1 | 82.1%* (110/134) |
| Acute myocardial infarction | Defined from admission diagnosis of acute myocardial infarction concurrently with coronary angiography or related death | ICD-10: I21, I22 | 86.5%† (4054/4688) |

PPV was represented as % (number of true positive cases / number of examined cases).
*We conducted a validation study using hospital administrative data from two tertiary hospitals.
†Validated in a study by Lee, HY. et al. (Atrial fibrillation and the risk of myocardial infarction: a nation-wide propensity-matched study. *Sci Rep* 2017;7(1):12716).
ICD-10, International Classification of Diseases-10th Revision; PPV, positive predictive value.

**Table S4. Baseline characteristics after propensity score matching.**

| Variables | Rhythm Control (N=5183) | Rate Control (N=5183) | ASD |
|---|---|---|---|
| **Sociodemographic** | | | |
| Age, years | 70 (62-76) | 70 (62-76) | <0.1% |
| <65 years | 1592 (30.7) | 1587 (30.6) | 0.2% |
| 65-74 year | 1921 (37.1) | 1940 (37.4) | 0.8% |
| ≥75 years | 1670 (32.2) | 1656 (32.0) | 0.6% |
| Male | 2862 (55.2) | 2894 (55.8) | 1.2% |
| AF duration, months | 0.5 (0.0-10.4) | 0.1 (0.0-13.1) | 2.1% |
| Enroll year | | | |
| 2011 | 342 (6.6) | 341 (6.6) | 0.1% |
| 2012 | 935 (18.0) | 950 (18.3) | 0.8% |
| 2013 | 1118 (21.6) | 1095 (21.1) | 1.1% |
| 2014 | 1215 (23.4) | 1205 (23.2) | 0.5% |
| 2015 | 1573 (30.3) | 1592 (30.7) | 0.8% |
| High tertile of income | 2250 (43.4) | 2277 (43.9) | 1.1% |
| Number of OPD visits ≥12/year | 4224 (81.5) | 4232 (81.7) | 0.4% |
| Living in metropolitan areas | 2322 (44.8) | 2306 (44.5) | 0.6% |
| Level of care initiating treatment | | | |
| Tertiary | 2544 (49.1) | 2503 (48.3) | 1.6% |
| Secondary | 2361 (45.6) | 2373 (45.8) | 0.5% |
| Primary | 278 (5.4) | 307 (5.9) | 2.4% |
| **Risk scores** | | | |
| $CHA_2DS_2$-VASc score | 4 (3-5) | 4 (3-5) | 0.9% |
| mHAS-BLED score* | 2 (2-3) | 2 (2-3) | 0.2% |
| Charlson comorbidity index | 4 (2-5) | 4 (2-5) | 0.3% |
| Hospital Frailty Risk score | 2.9 (0.3-6.6) | 2.6 (0.0-6.7) | 0.4% |
| **Medical history** | | | |
| Heart failure | 2817 (54.4) | 2815 (54.3) | 0.1% |
| Previous hospitalisation for heart failure | 748 (14.4) | 750 (14.5) | 0.1% |
| Hypertension | 4123 (79.5) | 4086 (78.8) | 1.8% |
| Diabetes | 1502 (29.0) | 1480 (28.6) | 0.9% |
| Dyslipidemia | 4287 (82.7) | 4258 (82.2) | 1.5% |
| Intracranial haemorrhage | 1777 (34.3) | 1779 (34.3) | 0.1% |
| Transient ischaemic attack | 496 (9.6) | 504 (9.7) | 0.5% |
| Haemorrhagic stroke | 132 (2.5) | 133 (2.6) | 0.1% |
| Myocardial infarction | 421 (8.1) | 415 (8.0) | 0.4% |
| Peripheral arterial disease | 744 (14.4) | 715 (13.8) | 1.6% |
| Valvular heart disease | 609 (11.7) | 607 (11.7) | 0.1% |
| Chronic kidney disease | 289 (5.6) | 295 (5.7) | 0.5% |
| Proteinuria | 386 (7.4) | 369 (7.1) | 1.3% |
| Hyperthyroidism | 502 (9.7) | 528 (10.2) | 1.7% |
| Hypothyroidism | 589 (11.4) | 612 (11.8) | 1.4% |
| Malignancy | 1241 (23.9) | 1229 (23.7) | 0.5% |
| COPD | 1617 (31.2) | 1635 (31.5) | 0.7% |
| Chronic liver disease | 2123 (41.0) | 2167 (41.8) | 1.7% |
| Hypertrophic cardiomyopathy | 68 (1.3) | 71 (1.4) | 0.5% |
| Osteoporosis | 1796 (34.7) | 1779 (34.3) | 0.7% |
| Sleep apnea | 29 (0.6) | 22 (0.4) | 1.9% |
| **Concurrent medication†** | | | |
| Oral anticoagulant | 5183 (100.0) | 5183 (100.0) | <0.1% |
| Warfarin | 4301 (83.0) | 4276 (82.5) | 1.3% |
| DOAC | 1155 (22.3) | 1199 (23.1) | 2.0% |
| Beta-blocker | 3797 (73.3) | 3644 (70.3) | 6.6% |

| | | | |
|---|---|---|---|
| Non-DHP CCB | 849 (16.4) | 818 (15.8) | 1.6% |
| Digoxin | 893 (17.2) | 1001 (19.3) | 5.4% |
| Aspirin | 1051 (20.3) | 1010 (19.5) | 2.0% |
| $P2Y_{12}$ inhibitor | 468 (9.0) | 478 (9.2) | 0.7% |
| Statin | 2394 (46.2) | 2355 (45.4) | 1.5% |
| DHP CCB | 816 (15.7) | 837 (16.1) | 1.1% |
| ACEI/ARB | 2790 (53.8) | 2806 (54.1) | 0.6% |
| Loop/thiazide diuretics | 2455 (47.4) | 2467 (47.6) | 0.5% |
| $K^+$ sparing diuretics | 983 (19.0) | 997 (19.2) | 0.7% |
| Alpha-blocker | 79 (1.5) | 105 (2.0) | 3.8% |

Values are presented as median (interquartile range) or n (%).

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

†Defined as a prescription fill of >90 days within the 180-day after the first prescription for rhythm- or rate-control drugs or the performance of an ablation procedure for AF.

AAD, antiarrhythmic drug; ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; ASD, absolute standardised difference; COPD, chronic obstructive pulmonary disease; DHP, dihydropyridine; DOAC, direct oral anticoagulant; OPD, outpatient department.

**Table S5. Definitions of 45 falsification endpoints.**

| Falsification endpoints | Definitions | ICD-10 codes / other conditions |
|---|---|---|
| Influenza | Defined from diagnosis plus treatment | J09, J10, J11 / Treatment: Oseltamivir |
| Major fracture | Defined from diagnosis on inpatient or emergency department record | S72, S72.0, S72.1, S72.2, S12.0, S12.1, S12.2, S12.7, S12.9, S22.0, S22.1, S32.0, S32 |
| Urinary tract infection | Defined from diagnosis* | N30, N300, N309, N341, N342, N390 |
| Fall accident | Defined from diagnosis on inpatient or emergency department record | W00-W19 |
| Tuberculosis | Defined from diagnosis* | A15, A16, A17, A18, A19 |
| Syphilis | Defined from diagnosis* | A50, A51, A52, A53 |
| Viral enteritis | Defined from diagnosis* | A08 |
| Warts | Defined from diagnosis* | B07 |
| Acute hepatitis A | Defined from diagnosis* | B15 |
| Viral conjunctivitis | Defined from diagnosis* | B30 |
| Stomach cancer | Defined from diagnosis* | C16 |
| Bone malignancy | Defined from diagnosis* | C40, C41, C90, C795 |
| Lymphoma | Defined from diagnosis* | C81, C82, C83, C84, C85 |
| Benign neoplasm of colon, rectum | Defined from diagnosis* | D12 |
| Lipoma | Defined from diagnosis* | D17 |
| Sleep apnea | Defined from diagnosis* | G473 |
| Carpal tunnel syndrome | Defined from diagnosis* | G560 |
| Hordeolum / chalazion | Defined from diagnosis* | H00 |
| Pterygium | Defined from diagnosis* | H110 |
| Glucoma | Defined from diagnosis* | H40, H42 |
| Otitis media | Defined from diagnosis* | H65, H66, H67 |
| Meniere's disease | Defined from diagnosis* | H810 |
| Benign paroxysmal positional vertigo | Defined from diagnosis* | H811 |
| Varicose veins of lower extremities | Defined from diagnosis* | I83 |
| Chronic sinusitis | Defined from diagnosis* | J32 |
| Nasal polyp | Defined from diagnosis* | J33 |
| Acute appendicitis | Defined from diagnosis on inpatient or emergency department record | K35 |
| Inguinal hernia | Defined from diagnosis* | K40 |
| Diverticulitis of intestine | Defined from diagnosis* | K57 |
| Cholecystitis | Defined from diagnosis* | K81 |
| Cellulitis | Defined from diagnosis* | L03 |
| Allergic contact dermatitis | Defined from diagnosis* | L23 |
| Urticaria | Defined from diagnosis* | L50 |
| Ingrowing nail | Defined from diagnosis* | L600 |
| Seropositive rheumatoid arthritis | Defined from diagnosis* | M05 |
| Spinal stenosis | Defined from diagnosis* | M480 |
| Frozen shoulder | Defined from diagnosis* | M750 |
| Osteomyelitis | Defined from diagnosis* | M86 |
| Nausea and vomiting | Defined from diagnosis* | R11 |
| Dysuria | Defined from diagnosis* | R30 |
| Voice disturbances | Defined from diagnosis* | R49 |
| Gout | Defined from diagnosis* | M10 |
| Burns | Defined from diagnosis* | T20-T32 |
| Anaphylaxis/Allergic reaction | Defined from diagnosis* | T78 |
| Traffic accident | Defined from diagnosis* | V01-V99 |

*To ensure accuracy, diagnosis was established based on one inpatient or two outpatient records of ICD-10 codes in the database. ICD-10, International Classification of Diseases, Tenth Revision.

**Table S6. Stratified analyses according to the initial choice of rhythm-control treatments: cardiovascular outcomes in weighted patients undergoing rhythm or rate control.**

| Outcome | Number of events | Person-years | Event rate | Number of events | Person-years | Event rate | Absolute rate difference per 100 person-years (95% CI) | Hazard ratio (95% CI) | P value |
|---|---|---|---|---|---|---|---|---|---|
| ***AAD vs. Rate control*** | | | | | | | | | |
| *Intention-to-treat* | AAD (N=12869) | | | Rate control (N=8982) | | | | | |
| Ischemic stroke | 695 | 28142 | 2.84 | 704 | 19379 | 3.66 | -0.82 (-1.38 to -0.25) | 0.78 (0.66–0.93) | 0.006 |
| Hospitalization for HF | 901 | 27875 | 3.67 | 856 | 19098 | 4.22 | -0.55 (-1.18 to 0.08) | 0.88 (0.75–1.03) | 0.116 |
| Acute myocardial infarction | 74 | 28958 | 0.23 | 64 | 20172 | 0.37 | -0.14 (-0.31 to 0.03) | 0.63 (0.35–1.13) | 0.118 |
| Cardiovascular death | 517 | 29035 | 2.25 | 532 | 20253 | 2.44 | -0.19 (-0.66 to 0.28) | 0.93 (0.76–1.14) | 0.472 |
| **Ablation vs. Rate control** | | | | | | | | | |
| *Intention-to-treat* | Ablation (N=784) | | | Rate control (N=8982) | | | | | |
| Ischemic stroke | 20 | 2086 | 0.75 | 704 | 19379 | 2.68 | -1.93 (-3.40 to -0.47) | 0.29 (0.11–0.80) | 0.017 |
| Hospitalization for HF | 20 | 2081 | 1.53 | 856 | 19098 | 3.16 | -1.63 (-3.35 to 0.09) | 0.51 (0.23–1.10) | 0.085 |
| Acute myocardial infarction | 4 | 2109 | 0.23 | 64 | 20172 | 0.29 | -0.06 (-0.62 to 0.50) | 0.83 (0.10–7.11) | 0.867 |
| Cardiovascular death | 6 | 2114 | 0.69 | 532 | 20253 | 1.50 | -0.81 (-1.96 to 0.34) | 0.48 (0.16–1.45) | 0.193 |

Event rates (per 100 person-years) and hazard ratios are overlap weighted.
AAD, antiarrhythmic drug; CI, confidence interval; HF, heart failure.

**Table S7. Cardiovascular outcomes in rhythm- and rate-controlled patients taking oral anticoagulants ≥80% of time at risk.**

| Outcome | Number of events | Person-years | Event rate | Number of events | Person-years | Event rate | Absolute rate difference per 100 person-years (95% CI) | Weighted hazard ratio (95% CI) | P value |
|---|---|---|---|---|---|---|---|---|---|
| ***Propensity overlap weighting*** | | | | | | | | | |
| *Intention to treat* | Rhythm control (N=8749) | | | Rate control (N=6410) | | | | | |
| Ischemic stroke | 429 | 18302 | 2.52 | 426 | 13863 | 3.17 | -0.65 (-1.30 to -0.00) | 0.79 (0.63–1.00) | 0.048 |
| Hospitalization for HF | 571 | 18132 | 3.50 | 532 | 13673 | 3.71 | -0.21 (-0.94 to 0.52) | 0.95 (0.77–1.16) | 0.594 |
| Acute myocardial infarction | 40 | 18810 | 0.20 | 26 | 14357 | 0.22 | -0.02 (-0.19 to 0.15) | 0.92 (0.40–2.11) | 0.849 |
| Cardiovascular death | 291 | 18848 | 1.90 | 296 | 14383 | 2.06 | -0.16 (-0.69 to 0.37) | 0.92 (0.71–1.20) | 0.547 |

Event rates (per 100 person-years) and hazard ratios are overlap weighted.
CI, confidence interval; HF, heart failure.

**Table S8. Risk of 45 falsification endpoints in weighted patients undergoing rhythm control compared with rate control.**

| Endpoints | HR (95% CI) | P value |
|---|---|---|
| Influenza | 0.89 (0.62-1.28) | 0.532 |
| Major fracture | 1.12 (0.90-1.38) | 0.316 |
| Urinary tract infection | 1.07 (0.97-1.19) | 0.183 |
| Fall accident | 1.01 (0.39-2.63) | 0.982 |
| Tuberculosis | 0.91 (0.72-1.15) | 0.415 |
| Syphilis | 0.67 (0.35-1.25) | 0.208 |
| Viral enteritis | 1.35 (0.79-2.32) | 0.275 |
| Warts | 0.79 (0.41-1.54) | 0.488 |
| Acute hepatitis A | 0.88 (0.37-2.05) | 0.761 |
| Viral conjunctivitis | 1.20 (0.75-1.93) | 0.444 |
| Stomach cancer | 0.87 (0.63-1.19) | 0.375 |
| Bone malignancy | 0.74 (0.44-1.26) | 0.265 |
| Lymphoma | 0.70 (0.30-1.66) | 0.418 |
| Benign neoplasm of colon, rectum | 1.32 (1.01-1.72) | 0.039 |
| Lipoma | 1.72 (0.96-3.06) | 0.067 |
| Sleep apnea | 1.51 (0.71-3.21) | 0.281 |
| Carpal tunnel syndrome | 0.64 (0.39-1.04) | 0.069 |
| Hordeolum | 1.10 (0.86-1.40) | 0.468 |
| Pterygium | 1.17 (0.78-1.76) | 0.447 |
| Glaucoma | 1.05 (0.95-1.16) | 0.363 |
| Otitis media | 1.05 (0.87-1.26) | 0.614 |
| Meniere's disease | 1.11 (0.83-1.49) | 0.489 |
| Benign paroxysmal positional vertigo | 1.05 (0.82-1.35) | 0.682 |
| Varicose veins of lower extremities | 0.94 (0.60-1.47) | 0.784 |
| Chronic sinusitis | 1.11 (0.94-1.30) | 0.213 |
| Nasal polyp | 1.50 (0.78-2.90) | 0.225 |
| Acute appendicitis | 1.40 (0.75-2.62) | 0.286 |
| Inguinal hernia | 1.11 (0.68-1.80) | 0.671 |
| Diverticulitis of intestine | 1.47 (0.83-2.62) | 0.187 |
| Cholecystitis | 0.91 (0.61-1.36) | 0.640 |
| Cellulitis | 1.09 (0.95-1.24) | 0.234 |
| Allergic contact dermatitis | 1.07 (0.98-1.17) | 0.153 |
| Urticaria | 1.07 (0.95-1.19) | 0.262 |
| Ingrowing nail | 1.06 (0.70-1.60) | 0.781 |
| Seropositive rheumatoid arthritis | 1.00 (0.85-1.17) | 0.970 |
| Spinal stenosis | 1.07 (0.97-1.18) | 0.206 |
| Frozen shoulder | 0.91 (0.79-1.06) | 0.226 |
| Osteomyelitis | 1.01 (0.44-2.31) | 0.975 |
| Nausea and vomiting | 1.10 (0.99-1.21) | 0.064 |
| Dysuria | 0.93 (0.75-1.16) | 0.533 |
| Voice disturbance | 1.32 (0.48-3.69) | 0.591 |
| Gout | 0.88 (0.67-1.17) | 0.367 |
| Burns | 1.24 (0.89-1.71) | 0.201 |
| Anaphylaxis/Allergic reaction | 0.99 (0.67-1.47) | 0.957 |
| Traffic accident | 0.83 (0.07-10.2) | 0.886 |

CI, confidence interval; HR, hazard ratio.

**Figure S1. Distributions of the propensity scores before and after overlap weighting.**

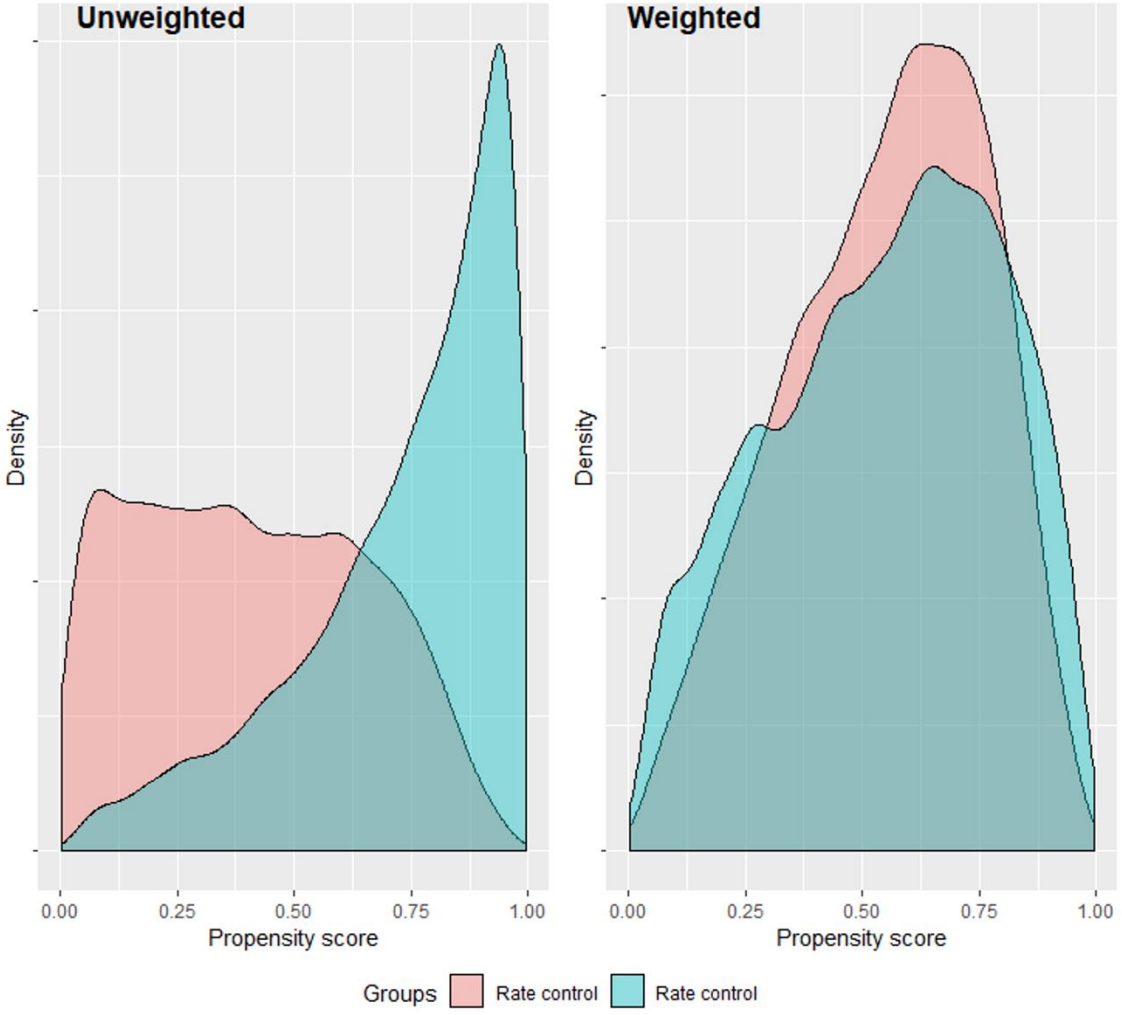
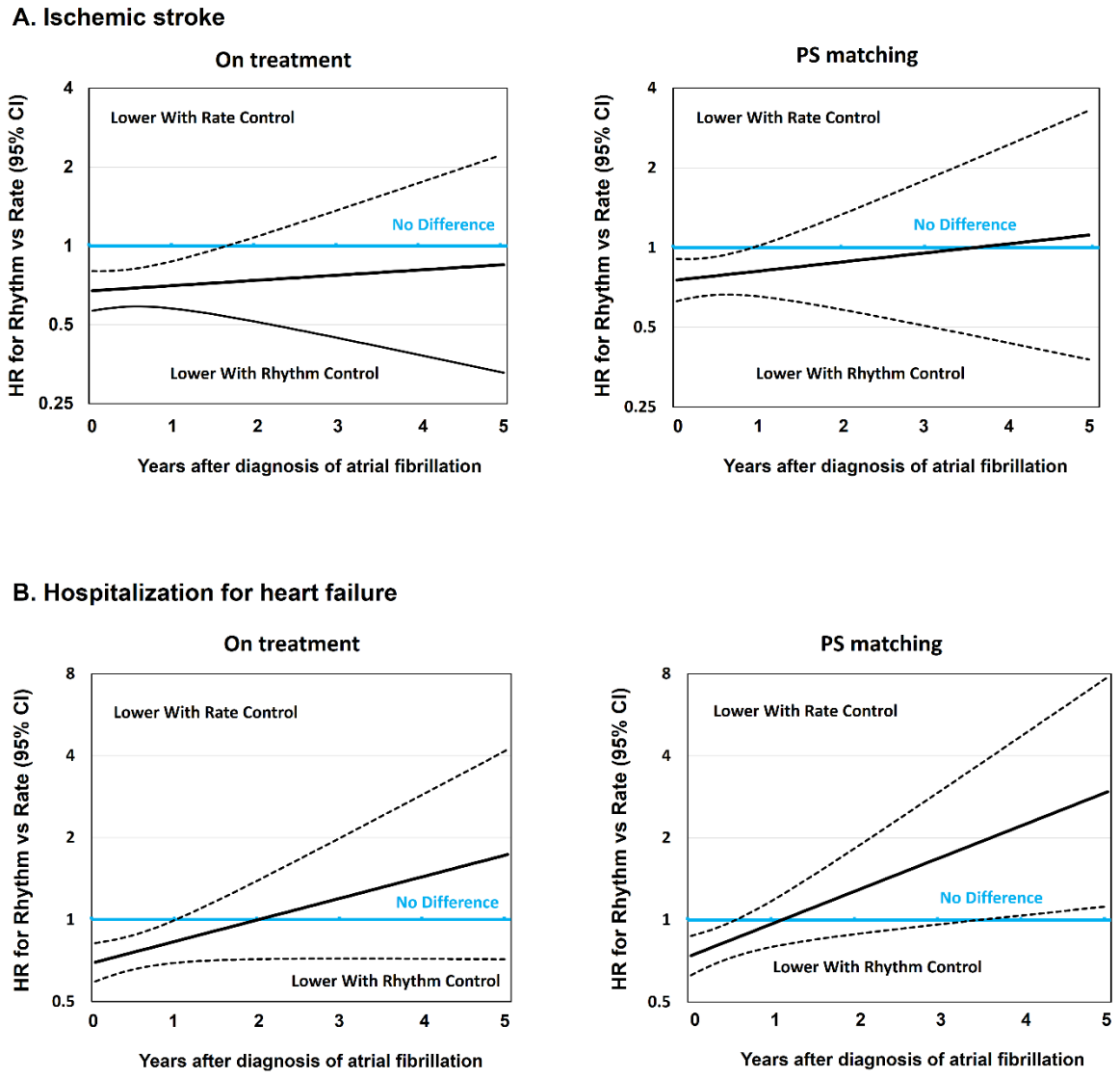
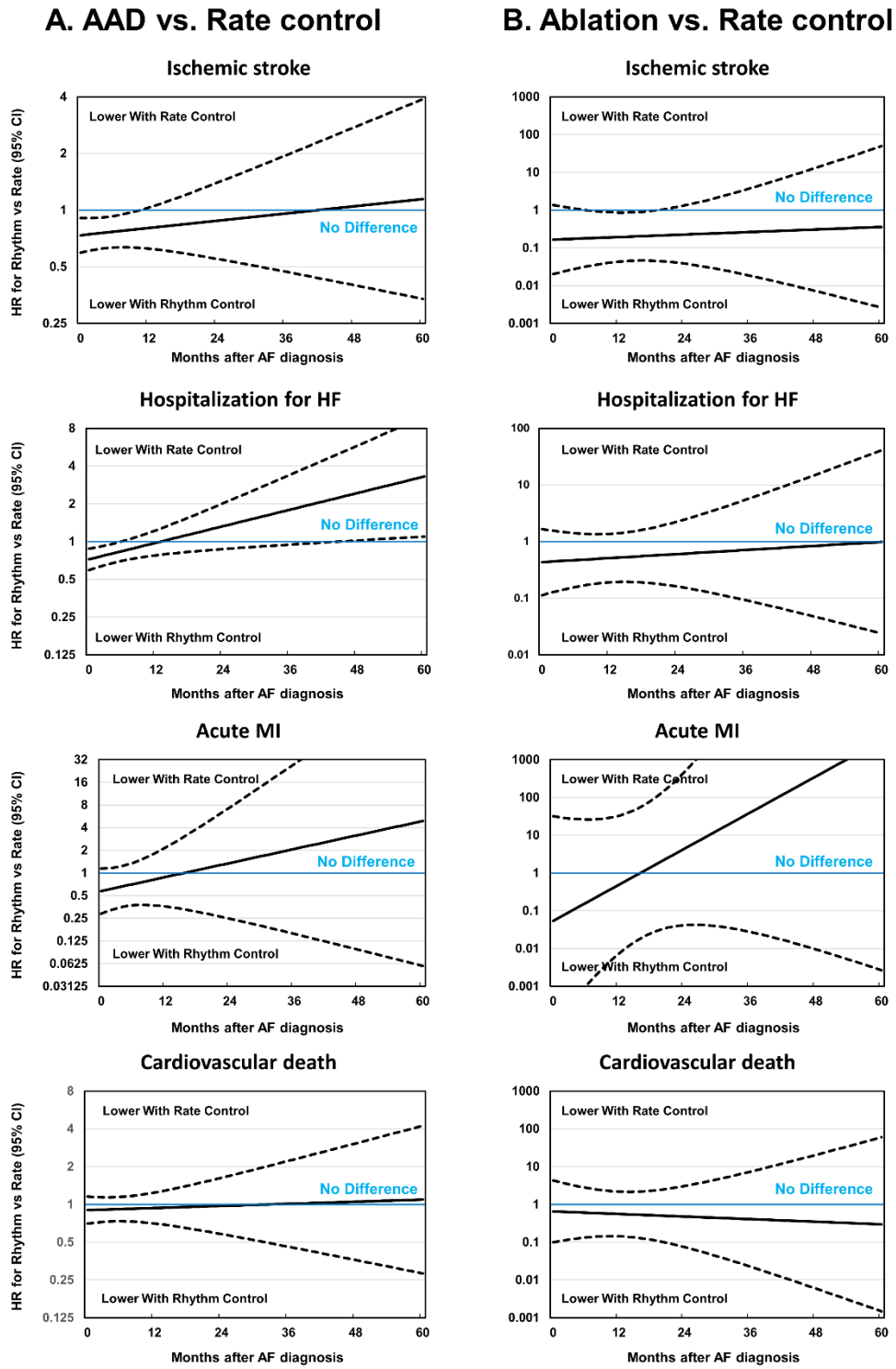


**Figure S2. Relation between treatment timing and risk of ischemic stroke (A) and hospitalization owing to heart failure (B) for rhythm control or rate control in on treatment analyses (overlap weighting) and propensity score matched analyses.**



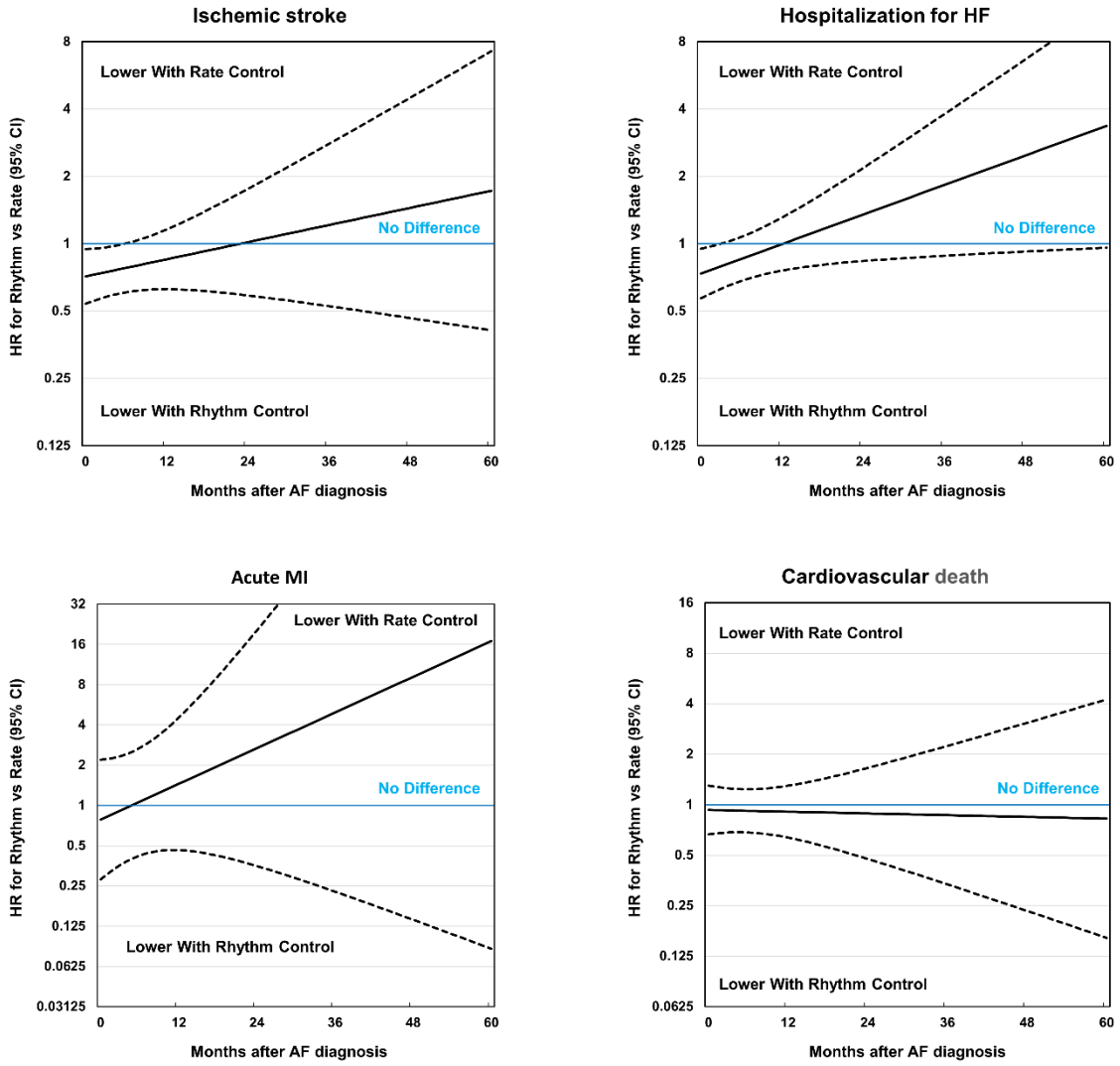

The x axis shows the timing of treatment initiation since the first diagnosis of atrial fibrillation; the y axis, hazard ratios (HRs) associated with rhythm control compared with rate control. The skyblue horizontal lines indicate HR=1, which corresponds to an equal risk of outcomes in patients treated with rhythm and rate control. Dashed black lines show the 95% confidence interval (CI).

**Figure S3. Stratified analyses according to the initial choice of rhythm-control treatments: relation between treatment timing and risk of cardiovascular outcomes for rhythm control or rate control.**




AAD, anti-arrhythmic drug; AF, atrial fibrillation; CI, confidence interval; HF, heart failure, HR, hazard ratio; MI, myocardial infarction.

**Figure S4. Relation between treatment timing and risk of cardiovascular outcomes for rhythm control or rate control among patients taking oral anticoagulants ≥80% of time at risk.**




AF, atrial fibrillation; CI, confidence interval; HF, heart failure, HR, hazard ratio; MI, myocardial infarction.