ORIGINAL ARTICLE

# Early Rhythm-Control Therapy in Patients with Atrial Fibrillation

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## ABSTRACT

### BACKGROUND

Despite improvements in the management of atrial fibrillation, patients with this condition remain at increased risk for cardiovascular complications. It is unclear whether early rhythm-control therapy can reduce this risk.

### METHODS

In this international, investigator-initiated, parallel-group, open, blinded-outcome-assessment trial, we randomly assigned patients who had early atrial fibrillation (diagnosed ≤1 year before enrollment) and cardiovascular conditions to receive either early rhythm control or usual care. Early rhythm control included treatment with antiarrhythmic drugs or atrial fibrillation ablation after randomization. Usual care limited rhythm control to the management of atrial fibrillation–related symptoms. The first primary outcome was a composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome; the second primary outcome was the number of nights spent in the hospital per year. The primary safety outcome was a composite of death, stroke, or serious adverse events related to rhythm-control therapy. Secondary outcomes, including symptoms and left ventricular function, were also evaluated.

### RESULTS

In 135 centers, 2789 patients with early atrial fibrillation (median time since diagnosis, 36 days) underwent randomization. The trial was stopped for efficacy at the third interim analysis after a median of 5.1 years of follow-up per patient. A first-primary-outcome event occurred in 249 of the patients assigned to early rhythm control (3.9 per 100 person-years) and in 316 patients assigned to usual care (5.0 per 100 person-years) (hazard ratio, 0.79; 96% confidence interval, 0.66 to 0.94; P=0.005). The mean (±SD) number of nights spent in the hospital did not differ significantly between the groups (5.8±21.9 and 5.1±15.5 days per year, respectively; P=0.23). The percentage of patients with a primary safety outcome event did not differ significantly between the groups; serious adverse events related to rhythm-control therapy occurred in 4.9% of the patients assigned to early rhythm control and 1.4% of the patients assigned to usual care. Symptoms and left ventricular function at 2 years did not differ significantly between the groups.

### CONCLUSIONS

Early rhythm-control therapy was associated with a lower risk of adverse cardiovascular outcomes than usual care among patients with early atrial fibrillation and cardiovascular conditions. (Funded by the German Ministry of Education and Research and others; EAST-AFNET 4 ISRCTN number, ISRCTN04708680; ClinicalTrials.gov number, NCT01288352; EudraCT number, 2010-021258-20.)

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Even with current guideline-based management, patients with atrial fibrillation have stroke, acute coronary syndrome, heart failure, and cardiovascular death at a rate of approximately 5% of patients per year,[1-4] and 35 to 50% of patients with atrial fibrillation who receive adequate anticoagulation either receive inpatient therapy or die within 5 years.[5,6] These complications occur even though most atrial fibrillation–related ischemic strokes can be prevented with anticoagulation,[3,4] and rate control often renders patients asymptomatic.[7,8] The risk of cardiovascular complications is increased during the first year after atrial fibrillation is diagnosed (a period referred to here as "early atrial fibrillation").[9] Furthermore, rhythm-control therapy may be more effective when delivered early.[10,11]

Previous trials, including one trial involving patients with heart failure, have not shown superiority of rhythm control with antiarrhythmic drugs over rate control in patients with established atrial fibrillation.[7,8,12,13] Small trials have suggested that atrial fibrillation ablation may improve left ventricular function and may reduce the risk of adverse outcomes in patients with atrial fibrillation and heart failure,[2,14] and in one trial the antiarrhythmic drug dronedarone, as compared with placebo, reduced the composite outcome of death and cardiovascular hospitalizations.[6] Some reports have indicated low rates of stroke and death associated with rhythm-control therapy,[5,15] including atrial fibrillation ablation.[16-18] The Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4) therefore was designed to test whether a strategy of early rhythm-control therapy that includes atrial fibrillation ablation would be associated with better outcomes in patients with early atrial fibrillation than contemporary, evidence-based usual care.[11]

## METHODS

### TRIAL DESIGN AND OVERSIGHT

We conducted an international, investigator-initiated, parallel-group, randomized, open, blinded-outcome-assessment trial. The details of the trial design have been published previously.[19] The trial protocol and statistical analysis plan are available with the full text of this article at NEJM.org. The trial was designed and overseen by an executive committee supported by a steering committee and was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice Guidelines. An independent data and safety monitoring board guided the trial. All serious adverse events were adjudicated by an independent end-point review committee, the members of which were not aware of the treatment-group assignments. The trial was planned by the Atrial Fibrillation Network (AFNET) and the European Heart Rhythm Association. AFNET was responsible for the conduct of the trial. The protocol was approved by the ethics review boards of all the institutions involved. Written informed consent was provided by all patients who participated in the trial.

AFNET conducted the trial while being advised by the trial committees and working with the contract research organization CRI — the Clinical Research Institute. The contract research organization and the study sites used the Marvin electronic case-report form system (XClinical). The Institute of Medical Biometry and Epidemiology at the University Medical Center Hamburg–Eppendorf served as the core statistical unit. The funders of the trial did not influence the trial design, data collection, analysis, or the decision to publish. The first author wrote the first draft of the manuscript. All voting members of the executive steering committee (see the Supplementary Appendix, available at NEJM.org) vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

### TRIAL POPULATION

We enrolled adults (≥18 years of age) who had early atrial fibrillation (defined as atrial fibrillation diagnosed ≤12 months before enrollment) and 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 (Modification of Diet in Renal Disease stage 3 or 4 [glomerular filtration rate, 15 to 59 ml per minute per 1.73 $m^2$ of body-surface area]), and left ventricular hypertrophy (diastolic septal wall width, >15 mm).

### TRIAL INTERVENTION

Treatment of cardiovascular conditions, anticoagulation, and rate control were mandated in all pa-

tients, in accordance with guideline recommendations.[20-22] Patients were randomly assigned in a 1:1 ratio to receive early rhythm control or usual care, with randomization stratified according to site and with variable block lengths used for concealment of assignments.

Early rhythm control required antiarrhythmic drugs or atrial fibrillation ablation, as well as cardioversion of persistent atrial fibrillation, to be initiated early after randomization. Local study teams chose the type of rhythm-control therapy independently to deliver this treatment, using protocol guidance based on current guidelines.[20-22] Patients who were randomly assigned to early rhythm-control therapy were asked to transmit a patient-operated single-lead electrocardiogram (ECG) (Vitaphone) twice per week and when symptomatic. All abnormal ECG recordings were forwarded to the study site. Documentation of recurrent atrial fibrillation triggered an in-person visit from the site team to escalate rhythm-control therapy as clinically indicated.

Patients who were randomly assigned to usual care were initially treated with rate-control therapy without rhythm-control therapy. Rhythm-control therapy was used only to mitigate uncontrolled atrial fibrillation–related symptoms during adequate rate-control therapy (i.e., therapy that maintained the heart rate within guideline-recommended targets).

### OUTCOMES AND ADVERSE EVENTS

The first primary outcome was a composite of death from cardiovascular causes, stroke (either ischemic and hemorrhagic), or hospitalization with worsening of heart failure or acute coronary syndrome, analyzed in a time-to-event analysis. The second primary outcome was the number of nights spent in the hospital per year. Secondary outcomes reported here include each component of the first primary outcome (analyzed in a time-to-event analysis), rhythm, left ventricular function, quality of life (assessed with the European Quality of Life–5 Dimensions [EQ-5D] visual analogue scale and the 12-Item Short-Form General Health Survey [SF-12]), atrial fibrillation–related symptoms (assessed as the European Heart Rhythm Association [EHRA] score), and cognitive function (based on the Montreal Cognitive Assessment [MoCA]) at 2 years. All the secondary outcomes are listed in Table S5 in the Supplementary Appendix.

The primary safety outcome was a composite of death from any cause, stroke, or prespecified serious adverse events of special interest capturing complications of rhythm-control therapy. Source data on all potential serious adverse events and adverse events of special interest were centrally adjudicated by the end-point review committee.

### FOLLOW-UP

All patients remained in follow-up from randomization until the end of the trial, death, or withdrawal from the trial. At baseline, a medical history; information on clinical characteristics, therapy, and symptom status (EHRA); responses on the MoCA, EQ-5D, and SF-12 questionnaires; and an ECG and echocardiogram were obtained. A blood specimen was obtained from patients who consented to participate in a biomarker substudy. Every 6 months, trial sites mailed questionnaires to all patients to obtain information on hospitalizations and cardiovascular events. Questionnaires were reviewed at the contract research organization, and source documents for all possible events were requested from the sites. At 1 and 2 years, an in-person interview, physical examination, and ECG were performed. The MoCA, EQ-5D, SF-12, and echocardiography were repeated at 2 years.

### STATISTICAL ANALYSIS

The trial was designed as an event-driven trial. The first and second primary outcomes were tested independently for differences between the treatment groups at an overall two-sided type 1 error rate of 4% for the first primary outcome and 1% for the second primary outcome to reach an overall type 1 error rate of 5%. A between-group difference of 20% in the annual rate of the first primary outcome was deemed a clinically relevant difference. We calculated that 685 events would be needed to show a 20% difference in the event rate for the first primary outcome with a power of 80%.

Under the assumption of an event rate of 8% per year in the control group, a recruitment time of 48 months, a minimum follow-up time of 24 months, and a loss-to-follow-up of 5% of the observation time, a sample of 2810 patients was calculated to be needed. After a prespecified blinded interim analysis of pooled event data that was performed after 42 months of recruitment, fol-

low-up time was increased to 30 months and the recruitment period to 65 months, resulting in a modified sample of 2745 patients without modifying the required number of events. Three unblinded interim analyses for early determination of significance were conducted by the data and safety monitoring board when 25%, 50%, and 75% of the required events of the first primary outcome had occurred.

The analyses of the primary outcomes included all patients who underwent randomization and at least one follow-up assessment. The analysis of the first primary outcome was a comparison of end-point review committee–adjudicated events between the treatment groups. The analysis followed a group-sequential design with three interim analyses with O'Brien–Fleming stopping boundaries and two-sided log-rank tests comparing early rhythm control with usual care. Deaths from noncardiovascular causes were treated as censored. Additional events at the termination of the trial were included with the use of the inverse normal method.[23] As the primary result of the trial, the two-sided P value based on Tsiatis, Rosner, and Mehta stagewise ordering, accompanied by the corresponding median unbiased estimate of the hazard ratio and 96% confidence interval, is given.[24]

The second primary outcome was calculated as the observed sum of nights in the hospital divided by the individual follow-up time (in days; in the case of a follow-up time of 0 days, 0.01 days of follow-up was assumed) and reported as annualized rates. The difference between the treatment groups was estimated as the arithmetic mean and t-based 99% confidence interval. For the primary analysis of the second primary outcome, a mixed negative binomial regression model was used. Explanations of the sensitivity analyses and analyses of secondary outcomes and further statistical details are provided in the Supplementary Appendix.

We used a multiple-imputation procedure with 60 imputations to replace missing values for continuous outcomes and covariates defined for adjustment. With the exception of the primary analysis, estimates are reported with two-sided 95% confidence intervals throughout (see the statistical analysis plan in the protocol). These confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects. All analyses were conducted with Stata software, version 16.1 (StataCorp), and R software, version 3.6.1 (R Project for Statistical Computing).

## RESULTS

### TRIAL PARTICIPANTS

A total of 2789 patients underwent randomization across 135 sites in 11 European countries between July 28, 2011, and December 30, 2016. The primary intention-to-treat population consisted of all 2789 patients — 1395 assigned to early rhythm control and 1394 assigned to usual care (Fig. 1). Most patients received guideline-recommended anticoagulation and therapy for cardiovascular conditions (Table 1). Patients were enrolled a median of 36 days (interquartile range, 6 to 112) after the first diagnosis of atrial fibrillation. Demographic and clinical characteristics were generally well balanced between the groups, although the use of digitalis glycosides and beta-blockers was slightly more common (probably because of the group assignment), and statin use slightly less common, among the patients assigned to usual care (Table 1, Fig. 1, and Table S3).

### INTERVENTION

Almost all patients (1323 [94.8%]) who were randomly assigned to early rhythm control received an antiarrhythmic drug or underwent atrial fibrillation ablation (Fig. 1), which replicated clinical practice patterns.[25] Among the 1395 patients, 216 (15.4%) had a triggered visit to adapt rhythm-control therapy. At 2 years, 908 of 1395 patients (65.1%) were still receiving rhythm-control therapy (Fig. 1).

Usual care consisted of treatment with rate-control therapy without rhythm-control therapy throughout follow-up in the majority of patients assigned to this group. Initially, 1335 (95.8%) of the 1394 patients in this group had their condition managed without rhythm-control therapy; at 2 years, 1191 of the 1394 patients (85.4%) were still not receiving rhythm-control therapy (Fig. 1).

Sinus rhythm was found more often in patients who had been randomly assigned to receive early rhythm control (84.9% at 1 year, 82.1% at 2 years) than in patients assigned to receive usual care (65.5% at 1 year, 60.5% at 2 years) (Table 2; imputed estimates are provided in Fig. S3). At 2 years, 1020 of 1159 patients (88.0%) assigned to early rhythm control and 1065 of 1171 patients

(90.9%) assigned to usual care were still taking oral anticoagulants.

### PRIMARY OUTCOMES

The trial was stopped for efficacy at the third interim analysis after a median follow-up of 5.1 years per patient. A first-primary-outcome event occurred in 249 patients assigned to receive early rhythm control (3.9 per 100 person-years) and in 316 patients assigned to receive usual care (5.0 per 100 person-years) (Table 2). When the results were adjusted for the group-sequential design of the

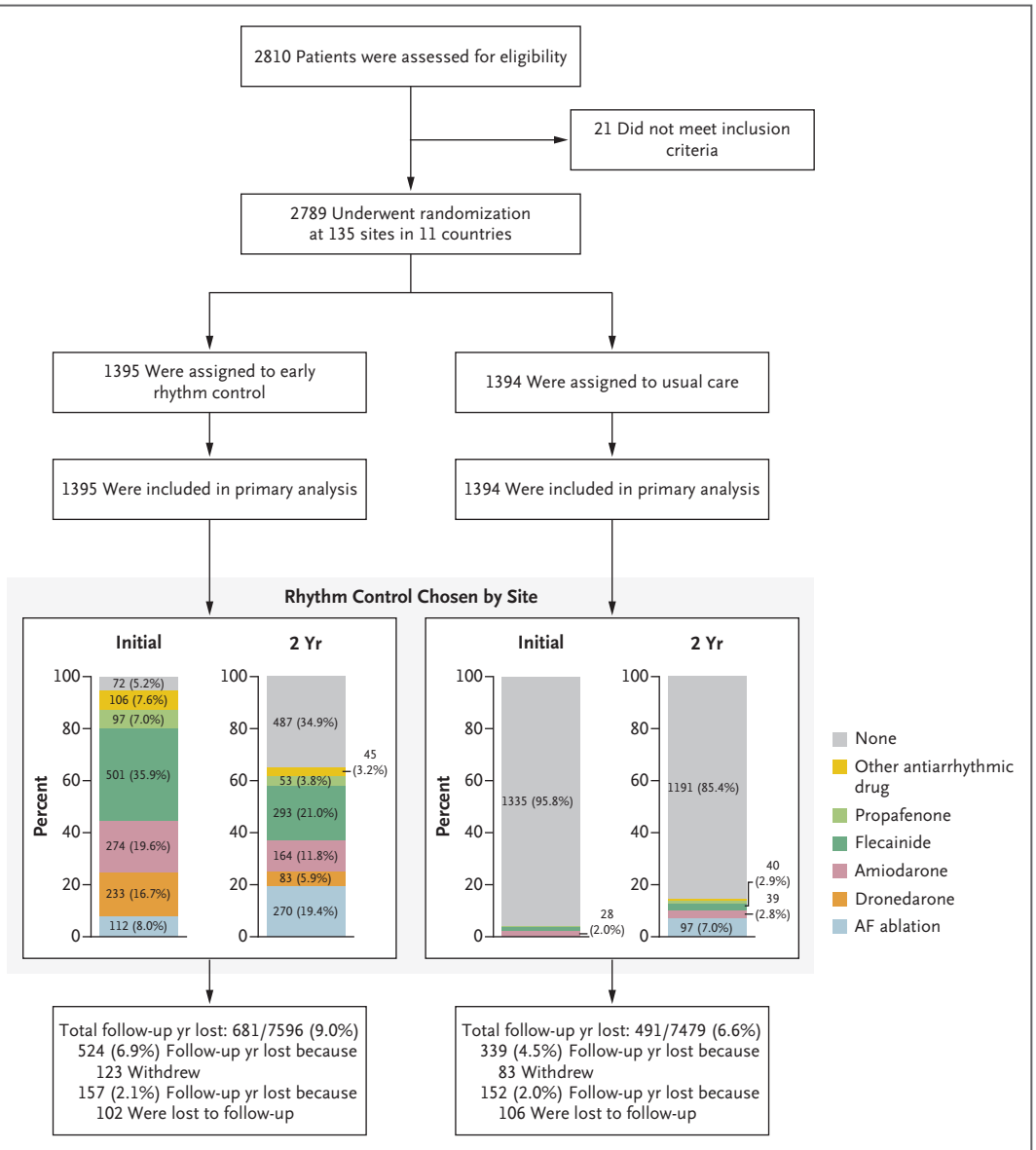



**Figure 1. Screening, Randomization, Treatment, and Follow-up.**

Most of the patients assigned to early rhythm-control therapy were initially treated with antiarrhythmic drugs, often flecainide. After 2 years of follow-up, 908 of the patients (65.1%) who had been randomly assigned to early rhythm-control therapy were still receiving active rhythm-control therapy (270 patients treated with atrial fibrillation [AF] ablation and 638 treated with antiarrhythmic drugs), and only 203 patients (14.6%) who had been randomly assigned to usual care were receiving rhythm-control therapy (97 treated with AF ablation and 106 treated with antiarrhythmic drugs). All patients who underwent randomization were included in the primary analysis.

**Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.***

| Characteristic | Early Rhythm Control (N=1395) | Usual Care (N=1394) |
|---|---|---|
| Age — yr | 70.2±8.4 | 70.4±8.2 |
| Female sex — no. (%) | 645 (46.2) | 648 (46.5) |
| Body-mass index† | 29.2±5.4 | 29.3±5.4 |
| Type of atrial fibrillation — no./total no. (%) | | |
| First episode | 528/1391 (38.0) | 520/1394 (37.3) |
| Paroxysmal | 501/1391 (36.0) | 493/1394 (35.4) |
| Persistent | 362/1391 (26.0) | 381/1394 (27.3) |
| Sinus rhythm at baseline — no./total no. (%) | 762/1389 (54.9) | 743/1393 (53.3) |
| Median days since atrial fibrillation diagnosis (IQR)‡ | 36.0 (6.0–114.0) | 36.0 (6.0–112.0) |
| Absence of atrial fibrillation symptoms — no./total no. (%)§ | 395/1305 (30.3) | 406/1328 (30.6) |
| Previous cardioversion — no./total no. (%) | 546/1364 (40.0) | 543/1389 (39.1) |
| **Concomitant cardiovascular conditions** | | |
| Previous stroke or transient ischemic attack — no. (%) | 175 (12.5) | 153 (11.0) |
| At least mild cognitive impairment — no./total no. (%)¶ | 582/1326 (43.9) | 584/1341 (43.5) |
| Arterial hypertension — no. (%) | 1230 (88.2) | 1220 (87.5) |
| Blood pressure — mm Hg‖ | | |
| Systolic | 136.5±19.4 | 137.5±19.3 |
| Diastolic | 80.9±12.1 | 81.3±12.0 |
| Stable heart failure — no. (%)** | 396 (28.4) | 402 (28.8) |
| $CHA_2DS_2$-VASc score†† | 3.4±1.3 | 3.3±1.3 |
| Valvular heart disease — no./total no. (%) | 609/1389 (43.8) | 642/1391 (46.2) |
| Chronic kidney disease of MDRD stage 3 or 4 — no. (%)‡‡ | 172 (12.3) | 179 (12.8) |
| Medication at discharge — no./total no. (%)§§ | | |
| Oral anticoagulation with NOAC or VKA | 1267/1389 (91.2) | 1250/1393 (89.7) |
| Digoxin or digitoxin | 46/1389 (3.3) | 85/1393 (6.1) |
| Beta-blocker | 1058/1389 (76.2) | 1191/1393 (85.5) |
| ACE inhibitors or angiotensin II receptor blocker | 953/1389 (68.6) | 979/1393 (70.3) |
| Mineralocorticoid-receptor antagonist | 90/1389 (6.5) | 92/1393 (6.6) |
| Diuretic | 559/1389 (40.2) | 561/1393 (40.3) |
| Statin | 628/1389 (45.2) | 568/1393 (40.8) |
| Platelet inhibitor | 229/1389 (16.5) | 226/1393 (16.2) |

* Plus–minus values are means ±SD. Definitions of clinical measures are provided in Table S1. ACE denotes angiotensin-converting enzyme, IQR interquartile range, NOAC non–vitamin K antagonist oral anticoagulant, and VKA vitamin K antagonist.

† The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were missing for 7 patients assigned to early rhythm control and for 6 patients assigned to usual care.

‡ Data on median days since atrial fibrillation diagnosis were missing for 2 patients assigned to early rhythm control and for 1 patient assigned to usual care.

§ The absence of symptoms was defined as a European Heart Rhythm Association (EHRA) score of I. The EHRA score categorizes symptoms related to atrial fibrillation into four classes from I (asymptomatic) to IV (severe symptoms at rest).

¶ At least mild cognitive impairment was defined as a Montreal Cognitive Assessment (MoCA) score of less than 26. The MoCA score provides an overall assessment of cognitive function. Scores range from 0 to 30, with lower scores indicating worse cognitive function.

‖ Data on blood pressure were missing for 9 patients assigned to early rhythm control and 4 patients assigned to usual care.

** Stable heart failure was defined as New York Heart Association stage II or a left ventricular ejection fraction of less than 50%.

†† $CHA_2DS_2$-VASc scores (an assessment of the risk of stroke among patients with atrial fibrillation) range from 0 to 9, with higher scores indicating a higher risk of stroke.

‡‡ A Modification of Diet in Renal Disease (MDRD) stage of 3 or 4 indicates a glomerular filtration rate of 15 to 59 ml per minute per 1.73 $m^2$ of body-surface area.

§§ Because of the high proportion of patients with atrial fibrillation that was first diagnosed at enrollment, important therapies were initiated between enrollment and discharge from the baseline visit. Therefore, medication at discharge from the baseline visit is shown.

**Table 2. Efficacy Outcomes.***

| Outcome | Early Rhythm Control | Usual Care | Treatment Effect |
|---|---|---|---|
| First primary outcome — events/person-yr (incidence/100 person-yr) | 249/6399 (3.9) | 316/6332 (5.0) | 0.79 (0.66 to 0.94)† |
| Components of first primary outcome — events/person-yr (incidence/100 person-yr) | | | |
| Death from cardiovascular causes | 67/6915 (1.0) | 94/6988 (1.3) | 0.72 (0.52 to 0.98)‡ |
| Stroke | 40/6813 (0.6) | 62/6856 (0.9) | 0.65 (0.44 to 0.97)‡ |
| Hospitalization with worsening of heart failure | 139/6620 (2.1) | 169/6558 (2.6) | 0.81 (0.65 to 1.02)‡ |
| Hospitalization with acute coronary syndrome | 53/6762 (0.8) | 65/6816 (1.0) | 0.83 (0.58 to 1.19)‡ |
| Second primary outcome — nights spent in hospital/yr | 5.8±21.9 | 5.1±15.5 | 1.08 (0.92 to 1.28)§ |
| Key secondary outcomes at 2 yr | | | |
| Change in left ventricular ejection fraction — % | 1.5±9.8 | 0.8±9.8 | 0.23 (–0.46 to –0.91)¶ |
| Change in EQ-5D score‖ | –1.0±21.4 | –2.7±22.3 | 1.07 (–0.68 to 2.82)¶ |
| Change in SF-12 Mental Score** | 0.7±10.6 | 1.6±10.1 | –1.20 (–2.04 to –0.37)¶ |
| Change in SF-12 Physical Score** | 0.3±8.5 | 0.1±8.2 | 0.33 (–0.39 to 1.06)¶ |
| Change in MoCA score | 0.1±3.3 | 0.1±3.2 | –0.14 (–0.39 to 0.12)¶ |
| Sinus rhythm — no. of patients with feature/total no. (%) | 921/1122 (82.1) | 687/1135 (60.5) | 3.13 (2.55 to 3.84)†† |
| Asymptomatic — no. of patients with feature/total no. (%)‡‡ | 861/1159 (74.3) | 850/1171 (72.6) | 1.14 (0.93 to 1.40)†† |

* Plus–minus values are means ±SD. Data in columns 2 and 3 are observed data, and data in column 4 are model-based effect estimates. There were no significant differences in the key secondary outcomes between the treatment groups, with two exceptions: more patients assigned to early rhythm control were in sinus rhythm at 2 years, and a slightly greater improvement in the 12-Item Short-Form Health Survey (SF-12) mental score at 2 years was found in the group assigned to usual care. All 95% confidence intervals for secondary end points were not adjusted for multiplicity and should not be used to infer definitive treatment effects. The results for additional secondary outcomes are provided in the Supplementary Appendix.

† The treatment effect is expressed as the median unbiased estimate of the hazard ratio and 96% confidence interval, which were calculated on the basis of Tsiatis, Rosner, and Mehta stagewise ordering that adjusts for the group-sequential design.[24] P=0.005 for the between-group comparison.

‡ The treatment effect is expressed as the hazard ratio and 95% confidence interval, which were calculated with a Cox regression with treatment group as the fixed factor and site as the shared frailty term.

§ The treatment effect is expressed as the incidence rate ratio and 99% confidence interval, which were calculated with a mixed negative binomial model with treatment group as the fixed factor, the log of follow-up time as the offset, and site as a random effect. P=0.23 for the between-group comparison.

¶ The treatment effect is expressed as the adjusted mean difference and 95% confidence interval, which were calculated with a mixed linear model with the corresponding baseline measurement and treatment group as the fixed effects and site as a random effect, analyzed after multiple imputation of missing values in survivors.

‖ The European Quality of Life–5 Dimensions (EQ-5D) assesses state of health on visual analogue scale from 0 (very bad health) to 100 (perfect health); values were defined as 0 for nonsurvivors.

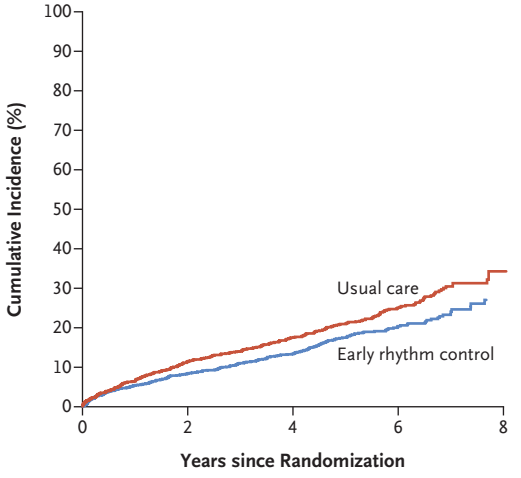
** Scores on the SF-12 range from 0 to 100, with lower scores indicating worse functioning.

†† The treatment effect is expressed as the odds ratio and 95% confidence interval, which were calculated with a mixed logistic regression including treatment group and the corresponding baseline assessment as fixed factors and site as a random effect, analyzed after multiple imputation of missing values in survivors.

‡‡ The absence of symptoms was defined as an EHRA score of I.

trial, a first-primary-outcome event was found to have occurred less often in patients assigned to early rhythm control than in patients assigned to usual care (hazard ratio, 0.79; 96% confidence interval [CI], 0.66 to 0.94; P=0.005) (Fig. 2). The effects of early rhythm control on individual components of the first primary outcome were consistent with the overall result (Table 2 and Fig. S4). The effect of early rhythm control on the first primary outcome remained stable after adjustment for relevant covariates (hazard ratio, 0.78; 95% CI, 0.66 to 0.92; P=0.004) (Fig. S1), and the effect was consistent across subgroups (Fig. S5). There was no significant difference in the mean (±SD) number of nights spent in the hospital between the treatment groups (early rhythm control, 5.8±21.9 days per year; usual care, 5.1±15.5 days per year; P=0.23) (Table 2).

The numbers of patients with a primary-safety-




| No. at Risk | | | | | |
|---|---|---|---|---|---|
| Usual care | 1394 | 1169 | 888 | 405 | 34 |
| Early rhythm control | 1395 | 1193 | 913 | 404 | 26 |

**Figure 2. Aalen–Johansen Cumulative-Incidence Curves for the First Primary Outcome.**

The first primary outcome was a composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome.

outcome event did not differ significantly between the treatment groups (early rhythm control, 231 patients; usual care, 223 patients) (Table 3 and Table S4). Mortality was similar in the two treatment groups, and stroke occurred less frequently among patients assigned to early rhythm control than among those assigned to usual care. Serious adverse events related to rhythm-control therapy were more common in the group assigned to early rhythm control but were infrequent; during the 5-year follow-up period, such events occurred in 68 patients (4.9%) assigned to early rhythm control and 19 patients (1.4%) assigned to usual care (Table 3 and Table S4).

### SECONDARY OUTCOMES

Left ventricular function and cognitive function were stable at 2 years, with no evidence of significant differences between the treatment groups (Table 2). Most patients in both groups were free from atrial fibrillation–related symptoms at 2 years, and the change from baseline in atrial fibrillation–related symptoms (EHRA score) and quality of life (EQ-5D score) did not differ significantly between the groups (Table 2).

## DISCUSSION

In this multicenter randomized trial, a strategy of initiating rhythm-control therapy in all patients with early atrial fibrillation and concomitant cardiovascular conditions was associated with a lower risk of death from cardiovascular causes, stroke, or hospitalization for heart failure or acute coronary syndrome than usual care over a follow-up time of more than 5 years (absolute difference in risk, 1.1 events per 100 person-years).

Early rhythm control did not affect the number of nights spent in the hospital. The absence of an appreciable difference in hospital nights is reassuring in view of the excess hospitalizations associated with rhythm-control therapy reported in two previous large trials.[8,13]

Most patients (>70%) were asymptomatic at 1 and 2 years in both treatment groups, and the magnitude of change in left ventricular function did not differ between the groups at 2 years, which indicates that both rate control and rhythm control can control symptoms and maintain cardiac function in patients with early atrial fibrillation. The effects of an early rhythm-control strategy on the primary outcome appeared to be generally consistent across predefined subgroups, including asymptomatic patients, patients with obesity, and patients with or without heart failure.

Previous studies comparing rate-control and rhythm-control strategies did not show better outcomes with rhythm control than with rate control.[7,8,12,13] In contrast to those trials, our trial included atrial fibrillation ablation, a powerful rhythm-control therapy[5,26] that works synergistically with antiarrhythmic drugs.[27,28] It is conceivable that atrial fibrillation ablation contributed to the superiority of early rhythm control in our trial. Also, unlike patients in previous trials,[7,8,12,13] most patients in both treatment groups in our trial continued to receive anticoagulation, rate control, and treatment of concomitant cardiovascular conditions, maintaining their protective effects.

Whereas previous trials have evaluated rhythm control in patients with established, long-standing atrial fibrillation,[7,8,12,13] we enrolled patients with early atrial fibrillation and initiated rhythm-control therapy shortly after the diagnosis of atrial fibrillation. Furthermore, 54% of the patients were in sinus rhythm at enrollment. In one large previous trial, rhythm-control therapy with

**Table 3. Safety Outcomes.***

| Outcome | Early Rhythm Control (N=1395) | Usual Care (N=1394) |
|---|---|---|
| | *number (percent)* | |
| Primary composite safety outcome | 231 (16.6) | 223 (16.0) |
| Stroke | 40 (2.9) | 62 (4.4) |
| Death | 138 (9.9) | 164 (11.8) |
| Serious adverse event of special interest related to rhythm-control therapy | 68 (4.9) | 19 (1.4) |
| Serious adverse event related to antiarrhythmic drug therapy | | |
| Nonfatal cardiac arrest | 1 (0.1) | 1 (0.1) |
| Toxic effects of atrial fibrillation–related drug therapy | 10 (0.7) | 3 (0.2) |
| Drug-induced bradycardia | 14 (1.0) | 5 (0.4) |
| Atrioventricular block | 2 (0.1) | 0 |
| Torsades de pointes tachycardia | 1 (0.1) | 0 |
| Serious adverse event related to atrial fibrillation ablation | | |
| Pericardial tamponade | 3 (0.2) | 0 |
| Major bleeding related to atrial fibrillation ablation | 6 (0.4) | 0 |
| Nonmajor bleeding related to atrial fibrillation ablation | 1 (0.1) | 2 (0.1) |
| Other serious adverse event of special interest related to rhythm-control therapy | | |
| Blood pressure–related event† | 1 (0.1) | 0 |
| Hospitalization for atrial fibrillation | 11 (0.8) | 3 (0.2) |
| Other cardiovascular event | 5 (0.4) | 1 (0.1) |
| Other event | 1 (0.1) | 3 (0.2) |
| Syncope | 4 (0.3) | 1 (0.1) |
| Hospitalization for worsening of heart failure with decompensated heart failure | 3 (0.2) | 0 |
| Implantation of a pacemaker, defibrillator, cardiac resynchronization device, or any other cardiac device | 8 (0.6) | 4 (0.3) |

* Patients could have had more than one event, and therefore the total sum of events is higher than the number of patients with events. For dichotomous outcomes, mixed logistic-regression models with a random effect for site were used for comparison of random groups. Stroke was significantly less frequent (P=0.03) and serious adverse events of special interest significantly more frequent (P<0.001) in the group assigned to early rhythm control; the other safety outcomes did not differ significantly between the groups.
† Blood pressure–related events included hypotension and hypertension (excluding syncope).

the antiarrhythmic drug dronedarone was found to reduce the risk of death or hospitalization for cardiovascular causes[6] and, in a post hoc analysis, was found to reduce the risk of stroke.[29] The majority of patients in that trial had had atrial fibrillation for less than 1 year (68% of the 2859 patients in whom the duration of atrial fibrillation was known), and 75% of the patients were in sinus rhythm at enrollment. Almost no patients were in sinus rhythm at the time of enrollment in another trial, in which harm was shown when dronedarone was tested in patients with chronic atrial fibrillation (most of whom had had atrial fibrillation for >2 years at enrollment).[30] Our results, together with other published evidence, suggest that the early initiation of rhythm-control therapy probably contributed to the clinical superiority of this strategy.

Early rhythm-control therapy used in the present trial included all major antiarrhythmic drugs and atrial fibrillation ablation, and there were no significant differences between the treatment groups with respect to the primary safety outcome. Early rhythm control was associated with more adverse events related to rhythm-control therapy than was usual care, but such events were uncommon, similar to the results of other recent trials comparing rhythm-control therapies in patients with atrial fibrillation.[5,26] Early initiation of rhythm-control therapy, guidance on the

safe use of antiarrhythmic drugs,[20-22] and the availability of atrial fibrillation ablation may have contributed to the low incidence of adverse events associated with rhythm-control therapy, as compared with previous trials.[7,8,12,13]

Some limitations of our trial should be noted. We compared two treatment strategies that necessitated an open trial design. Blinded, central assessment of primary outcomes was used to minimize bias. The trial was not primarily designed to assess the safety and effectiveness of specific components of early rhythm control. We enrolled only patients with early atrial fibrillation, and thus the results may not be generalizable to patients in whom rhythm-control therapy that includes atrial fibrillation ablation is initiated later. Further analysis is needed of the costs of early rhythm control. All enrolled patients were deemed eligible for either rate-control or rhythm-control therapy, which probably excluded the most symptomatic patients. We did not collect detailed information on recurrent atrial fibrillation in both groups, and therefore our data on percentages of patients with sinus rhythm are not comparable to data on recurrent atrial fibrillation from other rhythm-control trials.[5,11,26]

Early initiation of rhythm-control therapy was associated with less frequent cardiovascular events than usual care in patients with early atrial fibrillation and cardiovascular conditions without affecting the number of nights spent in the hospital. As expected, the early rhythm-control strategy was associated with more adverse events related to rhythm-control therapy, but the incidence of the overall safety outcome events was similar in the two groups. These results are relevant to decisions regarding rhythm-control therapy in patients with early atrial fibrillation.

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## APPENDIX

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