Journal of the American Heart Association

ORIGINAL RESEARCH

# Generalizability of the EAST-AFNET 4 Trial: Assessing Outcomes of Early Rhythm-Control Therapy in Patients With Atrial Fibrillation

Jannis Dickow, MD; Paulus Kirchhof, MD; Holly K. Van Houten, BA; Lindsey R. Sangaralingham, MPH; Leon H. W. Dinshaw, MD; Paul A. Friedman, MD; Douglas L. Packer, MD; Peter A. Noseworthy, MD; Xiaoxi Yao, PhD, MPH

**BACKGROUND:** EAST-AFNET 4 (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial) demonstrated clinical benefit of early rhythm-control therapy (ERC) in patients with new-onset atrial fibrillation (AF) and concomitant cardiovascular conditions compared with current guideline-based practice. This study aimed to evaluate the generalizability of EAST-AFNET 4 in routine practice.

**METHODS AND RESULTS:** Using a US administrative database, we identified 109 739 patients with newly diagnosed AF during the enrollment period of EAST-AFNET 4. Patients were classified as either receiving ERC, using AF ablation or antiarrhythmic drug therapy, within the first year after AF diagnosis (n=27 106) or not receiving ERC (control group, n=82 633). After propensity score overlap weighting, Cox proportional hazards regression was used to compare groups for the primary composite outcome of all-cause mortality, stroke, or hospitalization with the diagnoses heart failure or myocardial infarction. Most patients (79 948 of 109 739; 72.9%) met the inclusion criteria for EAST-AFNET 4. ERC was associated with a reduced risk for the primary composite outcome (hazard ratio [HR], 0.85; 95% CI, 0.75–0.97 [*P*=0.02]) with largely consistent results between eligible (HR, 0.89; 95% CI, 0.76–1.04 [*P*=0.14]) or ineligible (HR, 0.77; 95% CI, 0.60–0.98 [*P*=0.04]) patients for EAST-AFNET 4 trial inclusion. ERC was associated with lower risk of stroke in the overall cohort and in trial-eligible patients.

**CONCLUSIONS:** This analysis replicates the clinical benefit of ERC seen in EAST-AFNET 4. The results support adoption of ERC as part of the management of recently diagnosed AF in the United States.

**Key Words:** antiarrhythmic drugs ■ atrial fibrillation ■ cather ablation ■ rhythm-control therapy ■ trial generalizability

Atrial fibrillation (AF) is associated with an increased risk for cardiovascular complications such as death, stroke and myocardial infarction (MI), particularly in the first year after diagnosis.[1,2] Restoring and maintaining sinus rhythm has been associated with reduced mortality in large observational data sets[3]; however, previous randomized trials have failed to demonstrate superiority over rate control.[4–6] Recently, EAST-AFNET 4 (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial) randomized patients with recently diagnosed AF and increased cardiovascular risk ($CHA_2DS_2$-VASc score ≥2) to early rhythm-control therapy (ERC) or current guideline-based usual care, consisting of rate-control therapy initially with rhythm-control therapy added to improve AF–related symptoms.[7] In EAST-AFNET 4, which was stopped for efficacy, early rhythm control was associated with reduced risk in the composite end point of

Correspondence to: Xiaoxi Yao, PhD, MPH, Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. Email: Yao.Xiaoxi@mayo.edu

Supplemental Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.024214

For Sources of Funding and Disclosures, see page 10.



*JAHA* is available at: www.ahajournals.org/journal/jaha

## CLINICAL PERSPECTIVE

### What Is New?

- The majority of patients with newly diagnosed atrial fibrillation treated in routine US practice would be eligible for early rhythm control as tested in EAST-AFNET 4 (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial).

### What Are the Clinical Implications?

- Our data support the routine initiation of early rhythm-control therapy as part of the management of recently diagnosed atrial fibrillation in patients.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **AAD** | antiarrhythmic drug |
| **CABANA** | Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation |
| **EARLY-AF** | Early Aggressive Invasive Intervention for Atrial Fibrillation |
| **EAST-AFNET 4** | Early Treatment of Atrial Fibrillation for Stroke Prevention Trial |
| **ERC** | early rhythm control therapy |
| **STOP AF First** | Cryoballoon Catheter Ablation in an Antiarrhythmic Drug Naive Paroxysmal Atrial Fibrillation |

death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure (HF) or acute coronary syndrome (hazard ratio [HR], 0.79; 96% CI, 0.66 to 0.94]).[7] ERC included AF ablation in 25% of patients, added to continued anticoagulation and therapy for concomitant cardiovascular conditions. These characteristics distinguish EAST-AFNET 4 from prior "rhythm versus rate" strategy trials. Furthermore, rhythm control was initiated early, which may increase the effectiveness and safety of rhythm-control therapy.[8,9] Especially the early initiation of therapy raised questions with regards to the generalizability of the trial results in routine care.

To assess the generalizability of the EAST-AFNET 4 findings to routine practice in a large cohort of US patients with AF, we assessed the proportion of patients who would have met trial eligibility criteria and examined the association between early rhythm control and clinical outcomes, stratified by trial eligibility.

## METHODS

The Mayo Clinic's institutional review board exempted this study from review because it used preexisting, deidentified data. Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to OptumLabs.

### Study Population

This study was a retrospective cohort analysis using deidentified administrative claims data from the OptumLabs Data Warehouse, which contains medical and pharmacy claims and enrollment records for private insurance and Medicare Advantage enrollees of all ages and races throughout the United States.[10,11]

The study population included adult patients (aged ≥18 years) who had newly diagnosed AF between July 28, 2011, and December 30, 2016, the enrollment period of EAST-AFNET 4. Patients were divided into 2 treatment groups. The ERC group included patients who underwent ERC, ie, AF ablation or antiarrhythmic drug (AADs; Table S1) therapy, within the first year after AF diagnosis. Some patients were treated with both AF ablation and AADs. Cardioversion was not considered a chronic prophylactic treatment to prevent recurrence of AF and therefore not considered a criteria for ERC. AF ablation was identified using procedure codes (Table S2).[12,13] The control group included patients who did not receive rhythm-control therapy within the first year after AF diagnosis. These treatment groups approximated the randomized groups in EAST-AFNET 4. For analysis, the date 12 months after the first AF diagnosis was defined as the index date and the start of the follow-up period. The patient selection flow diagram is shown in Figure 1.

Enrolled patients in EAST-AFNET 4 (and the "trial-eligible" subgroup of the current study) who were either aged >75 years or had a previous transient ischemic attack or stroke, or met 2 of the following criteria: age >65 years, female sex, HF, hypertension, diabetes, severe coronary artery disease, chronic kidney disease (Modification of Diet in Renal Disease stage 3 or 4 [glomerular filtration rate, 15 to 59 mL/min per 1.73 $m^2$ of body surface area]), and left ventricular hypertrophy (diastolic septal wall width >15 mm).

Patients were required to have at least 12 months of continuous enrollment in health insurance plans before the first AF diagnosis date (baseline period) in order to capture an adequate medical history and to exclude those with AF diagnoses before the enrollment period. Also, patients were required to have AF diagnoses on at least 2 different days to exclude coding errors. Patients whose demographic or residence data were missing or invalid were excluded.

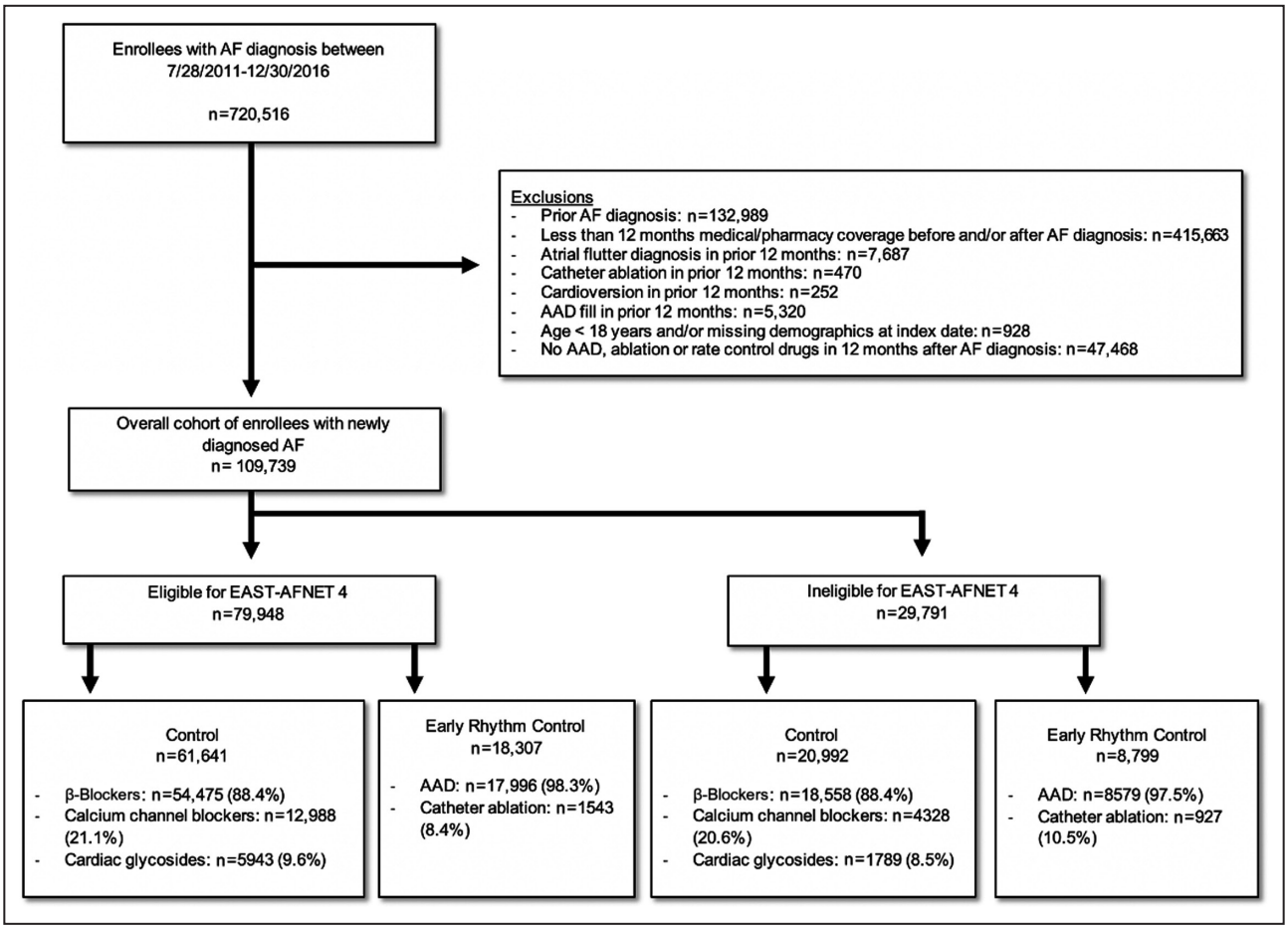



**Figure 1. Patient selection flow chart.**
From July 28, 2011, to December 30, 2016, the enrollment period of EAST-AFNET 4 (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial), we identified 109 739 patients with newly diagnosed atrial fibrillation (AF) (overall cohort). The majority of patients (72.9%; 79 948 of 109 739) would have been eligible for EAST-AFNET 4. AAD indicates antiarrhythmic drug.

## Outcomes

The primary outcome was a composite of all-cause mortality, stroke, or hospitalization with the diagnoses of HF or MI, ie, comparable to the primary outcome assessed in EAST-AFNET 4. The secondary outcomes included each of these outcomes considered separately. Mortality was identified based on the Social Security Death Master File and discharge status. Secondary analyses of administrative databases typically cannot ascertain the cause of death, therefore all-cause mortality was used rather than cardiovascular death. Patients were followed until December 31, 2019, the end of enrollment in health insurance plans, or death, whichever occurred first.

## Statistical Analysis

The proportion of patients who were not eligible for the trial was calculated and patients were divided into 3 subgroups based on the operational definition in Table S3: (1) patients who would be eligible for EAST-AFNET 4; (2) patients who failed to meet the inclusion criterion, ie, those aged <75 years without 2 stroke risk factors; and (3) patients who met at least one of the exclusion criteria. Some patients may have both failed to meet the inclusion criterion and met the exclusion criteria. Such patients were classified as those who met the exclusion criteria. In the stratified analyses for clinical outcomes, patients of subgroups 2 and 3 were summarized as patients ineligible for the trial.

Propensity score overlap weighting was used to balance differences in 83 baseline characteristics between patients who underwent ERC and controls in the overall cohort and in each subgroup stratified by trial egilibilty. The standardized mean difference was used to assess the balance of covariates after weighting and a difference <0.1 was considered acceptable.[14]

Cox proportional hazards regression was used to compare patients treated with ERC and controls in the propensity score–weighted cohort, with a robust sandwich estimator for variance estimation. The regression was performed in the overall cohort as well as in the

groups stratified by trial eligibility. The Fine and Gray method was used to consider death as a competing risk when assessing nonfatal outcomes (ie, stroke, or hospitalization with the diagnoses of HF or MI when considered separately).[15] The proportional hazards assumption was tested on the basis of Schoenfeld residuals.[16]

A 2-sided *P* value <0.05 was considered statistically significant for all tests. All analyses except those related to the primary outcome were considered to be exploratory and conducted using SAS Enterprise Guide 7.1 (SAS Institute Inc.) and Stata 16.0 (StataCorp).

## Sensitivity Analyses

We conducted several sensitivity analyses to assess the robustness of the findings. First, we performed subgroup analyses for the primary outcome stratified by age, sex, race, $CHA_2DS_2$-VASc score, hypertension with left ventricular hypertrophy, HF, cardiomyopathy, sleep apnea, and prior thromboembolism. Second, we conducted a stratified analysis based on whether patients with early rhythm control were treated with AF ablation or AADs only. Third, a similar stratified analysis was conducted based on the adherence to AADs in the early rhythm-control group. Adherence to AAD therapy was defined as the proportion of days covered ≥80%. Patients treated without early rhythm control were compared separately with those adherent and nonadherent AAD-treated patients. Last, we assessed residual confounding by testing 2 falsification end points that are unlikely to be a result of ERC but might be related to unmeasured confounders such as frailty: pneumonia and fracture. The prespecified analysis plan, including more details of the methods, is available in Data S1.

# RESULTS

## Patient Characteristics

We identified 109 739 patients with newly diagnosed AF from July 28, 2011, to December 30, 2016 (Table 1). The majority of patients (72.9%; 79 948 of 109 739) would have been eligible for EAST-AFNET 4 (Figure 1). Only 6926 patients (6.3%) failed to meet the trial inclusion criterion and 22 865 patients (20.8%) met the trial exclusion criteria. In the overall cohort, 27 106 patients (24.7%) received ERC, ie, AF ablation or AAD therapy, within the first year after AF diagnosis; 82 633 patients (75.3%) did not receive ERC. The mean age was 71.0±11.6 years, 52 417 patients (47.8%) were women, 21 582 patients (19.7%) had a history of stroke, and 76 921 patients (70.1%) had a $CHA_2DS_2$-VASc score of ≥4. Only 35 898 patients (32.7%) were using oral anticoagulation (before propensity score weighting: 29.2% in the control group and 43.4% in the early rhythm-control group; after propensity score weighting: 28.0% in the control group and 28.0% in the early rhythm-control group). The rates of catheter ablation among patients receiving ERC were similar in both trial-eligible (8.4%; 1543 of 18 307) and trial-ineligible (10.5%; 927 of 8799, Figure 1) patients. After propensity score weighting, patients receiving ERC and patients not receiving ERC were balanced on 83 dimensions (Table S4 through S6).

## Outcomes

Patients were followed for a mean of 2.6±1.8 years. In the overall cohort, ERC was associated with a reduction in the primary composite outcome of all-cause mortality, stroke, or hospitalization with the diagnoses HF or MI compared with the control group (9.45 versus 11.13 events per 100 person-years; HR, 0.85 [95% CI, 0.75–0.97]; *P*=0.02), and reduced risk for stroke (1.10 versus 1.70 events per 100 person-years; HR, 0.66 [95% CI, 0.47–0.93]; *P*=0.02) (Table 2 and Figure 2). There was no significant risk reduction for all-cause mortality (5.49 versus 6.24 events per 100 person-years; HR, 0.88 [95% CI, 0.75–1.04]; *P*=0.14) or hospitalization with the diagnoses HF (3.69 versus 3.94 events per 100 person-years; HR, 0.95 [95% CI, 0.76–1.18]; *P*=0.61) or MI (1.16 versus 1.52 events per 100 person-years; HR, 0.76 [95% CI, 0.54–1.08]; *P*=0.13). The observed results were largely consistent between patients eligible or ineligible for the trial; however, the reduction of stroke risk associated with ERC was only significant in patients eligible for the trial (1.27 versus 1.94 events per 100 person-years; HR, 0.67 [95% CI, 0.45–0.98]; *P*=0.04).

## Sensitivity Analyses

The risk reduction in the primary composite outcome associated with ERC was observed with significant differences in patients aged <75 years, patients with $CHA_2DS_2$-VASc scores ≥4, patients without systolic HF or cardiomyopathy, and patients with prior thromboembolism. Of note, the most significant interaction was observed by cardiomyopathy status (Figure 3). ERC was never associated with an increased risk in any of the outcomes analyzed or any of the subgroups (Table S7 through S10). Patients aged <75 years had significantly reduced stroke risk and reduced overall mortality. In patients eligible for the trial, event rates were highest and the risk reduction in the composite outcome was greatest in patients with prior thromboembolism. The subgroup analyses for the primary outcome stratified by trial eligibility can be found in Table S11 and Table S12.

In the stratified analysis based on whether patients with early rhythm control were treated with AF ablation or without AF ablation, ie, with AADs only, early rhythm control was associated with a lower risk of the primary

**Table 1. Selected Baseline Characteristics Before and After PS Weighting in the Overall Cohort**

| | Before PS weighting | | | After PS weighting | | |
|---|---|---|---|---|---|---|
| | Controls (n=82 633) | Early rhythm control (n=27 106) | Standardized difference | Controls (n=82 633) | Early rhythm control (n=27 106) | Standardized difference |
| Age, mean±SD, y | 71.7±11.6 | 68.9±11.4 | 0.245 | 70.1±12.3 | 70.1±11.9 | 0.000 |
| 18–64 | 24.5% | 33.6% | 0.202 | 29.9% | 29.9% | 0.000 |
| 65–74 | 27.4% | 30.9% | 0.077 | 26.5% | 26.5% | 0.000 |
| 75+ | 48.1% | 35.5% | 0.258 | 43.6% | 43.6% | 0.000 |
| Women | 50.1% | 40.8% | 0.188 | 40.3% | 40.3% | 0.000 |
| Race or ethnicity | | | | | | |
| Asian | 2.5% | 2.0% | 0.031 | 2.7% | 2.7% | 0.000 |
| Black | 11.7% | 8.8% | 0.094 | 10.2% | 10.2% | 0.000 |
| Hispanic | 6.6% | 5.6% | 0.042 | 7.0% | 7.0% | 0.000 |
| Unknown | 2.4% | 2.4% | 0.001 | 2.2% | 2.2% | 0.000 |
| White | 76.8% | 81.1% | 0.105 | 77.9% | 77.9% | 0.000 |
| Comorbidities | | | | | | |
| Systolic HF | 16.9% | 22.5% | 0.142 | 25.7% | 25.7% | 0.000 |
| Cardiomyopathy | | | | | | |
| None | 80.4% | 74.9% | 0.133 | 68.9% | 68.9% | 0.000 |
| Hypertrophic | 1.3% | 1.7% | 0.032 | 2.7% | 2.7% | 0.000 |
| Ischemic | 4.6% | 6.0% | 0.060 | 8.1% | 8.1% | 0.000 |
| Dilated | 13.6% | 17.4% | 0.105 | 20.3% | 20.3% | 0.000 |
| Implanted device | | | | | | |
| None | 87.1% | 85.3% | 0.053 | 75.1% | 75.1% | 0.000 |
| CRT defibrillator | 0.6% | 0.9% | 0.038 | 1.9% | 1.9% | 0.000 |
| ICD | 5.2% | 5.6% | 0.019 | 12.3% | 12.3% | 0.000 |
| CRT pacemaker | 0.1% | 0.1% | 0.002 | 0.3% | 0.3% | 0.000 |
| Dual-chamber pacemaker | 5.3% | 5.9% | 0.025 | 7.5% | 7.5% | 0.000 |
| Single-chamber pacemaker | 1.8% | 2.3% | 0.033 | 3.0% | 3.0% | 0.000 |
| Hypertension | 94.0% | 90.7% | 0.123 | 92.2% | 92.2% | 0.000 |
| Diabetes | 42.7% | 36.7% | 0.123 | 44.3% | 44.3% | 0.000 |
| Thromboembolism | 26.2% | 20.7% | 0.130 | 25.4% | 25.4% | 0.000 |
| Stroke | 21.0% | 15.6% | 0.139 | 20.1% | 20.1% | 0.000 |
| CAD | 62.0% | 65.5% | 0.071 | 74.9% | 74.9% | 0.000 |
| Myocardial infarction | 24.8% | 26.1% | 0.032 | 34.0% | 34.0% | 0.000 |
| Left ventricular hypertrophy | 33.6% | 40.7% | 0.149 | 41.3% | 41.3% | 0.000 |
| Prior valve procedure | 2.9% | 9.5% | 0.274 | 6.4% | 6.4% | 0.000 |
| Mitral stenosis | 2.6% | 3.7% | 0.063 | 4.4% | 4.4% | 0.000 |
| Mitral regurgitation | 40.1% | 50.5% | 0.210 | 49.1% | 49.1% | 0.000 |
| Major bleeding | 31.5% | 30.4% | 0.023 | 32.0% | 32.0% | 0.000 |
| Intracranial bleeding | 3.6% | 2.9% | 0.041 | 3.2% | 3.2% | 0.000 |
| Stage 3–5 CKD | 20.0% | 17.3% | 0.069 | 20.4% | 20.4% | 0.000 |
| COPD | 24.6% | 23.0% | 0.037 | 25.5% | 25.5% | 0.000 |
| Obstructive sleep apnea | 21.7% | 28.7% | 0.164 | 27.4% | 27.4% | 0.000 |
| Previous drug treatment | | | | | | |
| No. of previous AADs | | | | | | |
| 0 | 99.2% | 1.9% | 8.365 | 31.2% | 31.2% | 0.000 |
| 1 | 0.8% | 88.6% | 3.757 | 67.0% | 67.0% | 0.000 |
| 2+ | 0.0% | 9.5% | 0.457 | 1.7% | 1.7% | 0.000 |

(*Continued*)

**Table 1. Continued**

| | Before PS weighting | | | After PS weighting | | |
|---|---|---|---|---|---|---|
| | Controls (n=82 633) | Early rhythm control (n=27 106) | Standardized difference | Controls (n=82 633) | Early rhythm control (n=27 106) | Standardized difference |
| Amiodarone use | 0.6% | 58.7% | 1.651 | 47.5% | 47.5% | 0.000 |
| No. of previous rate control drugs | | | | | | |
| 0 | * | * | 0.466 | 0.2% | 0.2% | 0.000 |
| 1 | 61.1% | 48.4% | 0.258 | 48.3% | 48.3% | 0.000 |
| 2 | 28.4% | 29.0% | 0.012 | 33.1% | 33.1% | 0.000 |
| 3+ | * | * | 0.075 | 18.3% | 18.3% | 0.000 |
| Concurrent Medication | | | | | | |
| Oral anticoagulants | | | | | | |
| None | 70.8% | 56.6% | 0.298 | 72.0% | 72.0% | 0.000 |
| Warfarin | 14.8% | 15.8% | 0.027 | 12.6% | 12.6% | 0.000 |
| NOAC | 14.4% | 27.6% | 0.329 | 15.4% | 15.4% | 0.000 |
| ACEIs | 28.2% | 26.7% | 0.034 | 28.3% | 28.3% | 0.000 |
| ARBs | 17.4% | 17.1% | 0.008 | 17.9% | 17.9% | 0.000 |
| β-Blockers (rate control) | 70.0% | 53.2% | 0.350 | 67.2% | 67.2% | 0.000 |
| Calcium channel blockers (rate control) | 14.3% | 10.5% | 0.118 | 10.8% | 10.8% | 0.000 |
| Digitalis | 6.4% | 4.3% | 0.093 | 6.9% | 6.9% | 0.000 |
| Statin | 48.7% | 48.3% | 0.009 | 52.1% | 52.1% | 0.000 |
| Insulin | 8.8% | 6.2% | 0.100 | 9.8% | 9.8% | 0.000 |
| $CHA_2DS_2$-VASc, mean±SD | 4.7±2.0 | 4.3±2.1 | 0.224 | 4.7±2.1 | 4.7±2.1 | 0.000 |

AAD indicates antiarrhythmic drug; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CAD; coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter–defibrillator; HF, heart failure; NOAC, non–vitamin K antagonist oral anticoagulant; and PS, propensity score.

*To maintain deidentification, OptumLabs does not allow researchers to disclose the number of events when the number is ≤10.

composite end point in patients treated without AF ablation (11.39 versus 13.28 events per 100 person-years; HR, 0.86 [95% CI, 0.74–1.00]; *P*=0.05) but not in patients treated with AF ablation; however, event rates were much lower in these patients and this subsample was relatively small (4.36 versus 5.40 events per 100 person-years; HR, 0.80 [95% CI, 0.55–1.18]; *P*=0.26) (Table S13).

For patients in the early rhythm-control group who adhered to AAD therapy, ERC was associated with a lower stroke risk in both the overall cohort and in trial-eligible patients, but the magnitude was greater in trial-eligible patients (0.92 versus 2.15 events per 100 person-years; HR, 0.43 [95% CI, 0.25–0.74]; *P*<0.01) (Table S14 through Table S16).

There was no difference in the rate of fracture or pneumonia, the chosen falsification end points between patients treated with early rhythm control and control patients (Table S17).

## DISCUSSION

In this large US data set of 109 739 patients with newly diagnosed AF, ERC was associated with a lower risk of death, stroke, or hospitalization with the diagnoses HF or MI, with the greatest reduction in stroke risk. The majority of patients (72.9%; 79 948 of 109 739) treated in routine US practice appear to meet enrollment criteria for EAST-AFNET 4 and the observed results associated with ERC in routine practice are largely consistent between patients eligible or ineligible for the trial.

Patients in routine practice had higher rates of adverse outcomes than the trial, but the relative risk reduction with ERC was similar: EAST-AFNET 4 reported a 21% reduction in the composite end point associated with early rhythm control, with low overall event rates of 3.9 events per 100 person-years in the early rhythm-control group and 5.0 events per 100 person-years in the usual care group.[7] Event rates in this analysis were higher, but the relative stroke risk reduction associated with ERC observed in routine practice of 34% is consistent with EAST-AFNET 4. Absolute stroke rates were higher in this analysis than in the trial, possibly because of the lower rate of anticoagulation (≈90% in EAST-AFNET 4 compared with only 32.7% of patients in this data set). Furthermore, patients in this analysis had more cardiovascular comorbidities (the mean $CHA_2DS_2$-VASc score was 4.6 in OptumLabs compared with 3.4 in EAST-AFNET 4). Interestingly, the

**Table 2. Outcomes in PS–Weighted Patients Stratified by Trial Eligibility**

| Control | | | | Early rhythm control | | | | |
|---|---|---|---|---|---|---|---|---|
| | No. of events | Person-years | Event rate | No. of events | Person-years | Event rate | HR (95% CI) | *P* value |
| Overall cohort | n= 82 633 | | | n=27 106 | | | | |
| Composite | 228 | 2049 | 11.13 | 195 | 2065 | 9.45 | 0.85 (0.75–0.97) | 0.015 |
| Stroke | 37 | 2185 | 1.70 | 24 | 2191 | 1.10 | 0.66 (0.47–0.93) | 0.017 |
| HF | 84 | 2125 | 3.94 | 78 | 2124 | 3.69 | 0.95 (0.76–1.18) | 0.613 |
| MI | 34 | 2203 | 1.52 | 25 | 2188 | 1.16 | 0.76 (0.54–1.08) | 0.127 |
| Mortality | 140 | 2243 | 6.24 | 122 | 2223 | 5.49 | 0.88 (0.75–1.04) | 0.135 |
| Eligible for trial | n=61 641 | | | n=18 307 | | | | |
| Composite | 165 | 1507 | 10.98 | 143 | 1466 | 9.76 | 0.89 (0.76–1.04) | 0.138 |
| Stroke | 31 | 1598 | 1.94 | 20 | 1560 | 1.27 | 0.67 (0.45–0.98) | 0.041 |
| HF | 56 | 1566 | 3.60 | 56 | 1512 | 3.67 | 1.03 (0.79–1.34) | 0.843 |
| MI | 26 | 1613 | 1.59 | 19 | 1558 | 1.24 | 0.78 (0.53–1.17) | 0.236 |
| Mortality | 102 | 1644 | 6.23 | 86 | 1586 | 5.40 | 0.87 (0.72–1.06) | 0.168 |
| Ineligible for trial | n=20 992 | | | n=8799 | | | | |
| Composite | 63 | 543 | 11.55 | 52 | 600 | 8.69 | 0.77 (0.60–0.98) | 0.035 |
| Stroke | 6 | 587 | 1.04 | 4 | 631 | 0.69 | 0.67 (0.33–1.34) | 0.254 |
| HF | 27 | 560 | 4.89 | 23 | 611 | 3.73 | 0.79 (0.54–1.15) | 0.214 |
| MI | 8 | 589 | 1.35 | 6 | 630 | 0.94 | 0.71 (0.36–1.41) | 0.330 |
| Mortality | 37 | 599 | 6.25 | 36 | 637 | 5.69 | 0.92 (0.68–1.26) | 0.621 |

The event rate was calculated as the number of events per 100 person-years. Propensity score (PS) weight was applied when calculating number of events, person-years, event rates, absolute reduction, and hazard ratios (HRs). HF indicates hospitalization with the diagnosis of heart failure; and MI, hospitalization with the diagnosis of myocardial infarction.

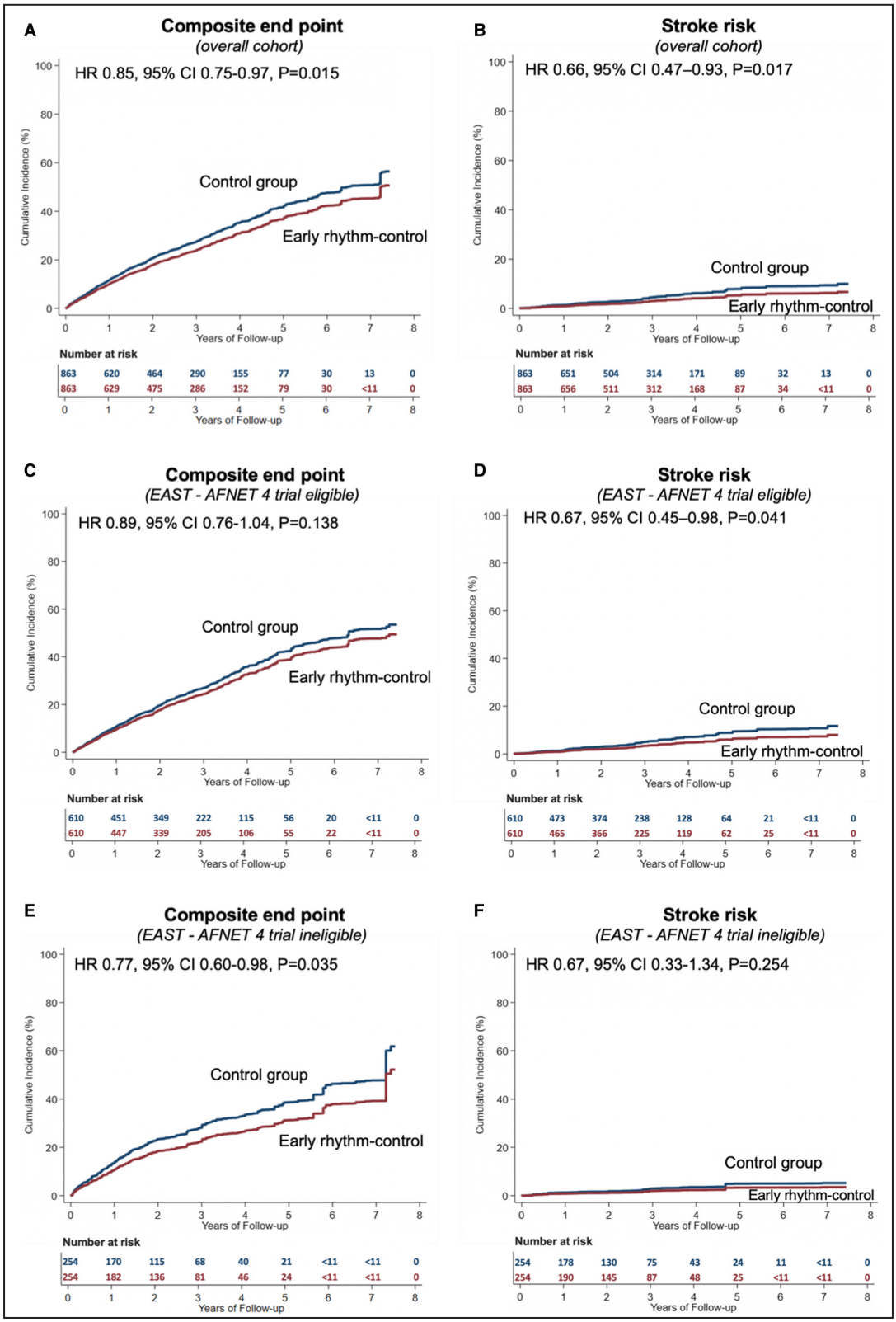
mean age was quasi-identical to the EAST-AFNET 4 population (70.2±8.4 years). In addition, differences in absolute event rates could be related to the different methods of event adjudication/ascertainment between retrospective claims–based analyses and prospective trial event classification.

AF ablation was used in a minority of patients treated with early rhythm control (≈1 in 10 patients), similar to EAST-AFNET 4. Patients treated with AF ablation in this data set had a lower event rate, most likely reflecting the clinical tendency to offer AF ablation to younger and healthier patients as reflected by lower age and $CHA_2DS_2$-VASc scores. The lower event rate and the lower number of patients are likely reasons that the risk reduction associated with early rhythm control showed a comparable hazard rate but no statistical significance (HR, 0.80; 95% CI, 0.55–1.18) compared with control. Adding to earlier reports assessing AF ablation as first-line rhythm-control therapy,[17] the recently published EARLY-AF (Early Aggressive Invasive Intervention for Atrial Fibrillation) and STOP AF First (Cryoballoon Catheter Ablation in an Antiarrhythmic Drug Naive Paroxysmal Atrial Fibrillation) trials both demonstrated the safety of AF ablation using cryoballoon devices compared with AAD therapy with lower AF recurrence rates.[18,19] Consistent with these findings and with the safety profile of AAD and AF ablation therapy in the CABANA (Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation) trial,[20] none of our analyses found a signal for harm associated with early rhythm control.

This is the largest comparison of patients treated with ERC and controls, including >100 000 patients. The strengths of the study are the close modeling of the EAST-AFNET 4 inclusion criteria and the well-documented information on events. The estimate for eligibility thus should be robust. Taken together with the main findings from the EAST-AFNET 4 randomized clinical trial and with a recent analysis in the Korean Health Data showing lower event rates in Korean patients treated with ERC (early rhythm control 7.42 events per 100 patient-years, controls 9.25 events per 100 patient-years; HR, 0.81 [95% CI, 0.71–0.93]),[21] our data support the inclusion of ERC in the management of all patients with recently diagnosed AF and concomitant conditions to avoid missing positive effects, calling for an update of international guidelines.[22,23]

## Limitations

First, the comparison between treatment groups was not randomized and is therefore prone to residual confounding despite careful adjustment.[12,13] However, many of the measured variables are strongly correlated with unmeasured variables and the propensity matching procedure used here resulted in identical values on 83 baseline characteristics. Furthermore, the lack of effect of early rhythm control of other health outcomes (pneumonia, fracture) associated with frailty and




multimorbidity support the robustness of our matching algorithms.

Second, administrative data can be subject to misclassification. However, the billing codes used in this study are robustly monitored by payors and hospitals during the reimbursement process and have been commonly used and have demonstrated good performance in validation studies with positive predictive values around 90%.[24–28] The information contained in health data sets such as OptumLabs is less precise

**Figure 2. Primary composite end point and cumulative incidence of stroke stratified by EAST-AFNET 4 (Early treatment of atrial fibrillation for stroke prevention trial) eligibility criteria.**
Cumulative incidence curves for the primary outcome, a composite of all-cause mortality, stroke, or hospitalization with the diagnoses of heart failure or myocardial infarction in the early rhythm-control group (red) or control group (blue), stratified by EAST-AFNET 4 trial eligibility criteria. Overall cohort (**A** and **B**), patients who would be potentially eligible for EAST-AFNET 4 (**C** and **D**), and patients who would be ineligible for EAST-AFNET 4 (**E** and **F**). The control group was the reference group in the Cox proportional hazards regression analyses. All of the curves and numbers were calculated using propensity score weighting. *To maintain deidentification, OptumLabs does not allow researchers to disclose the number of events when the number is ≤10. HR indicates hazard ratio.

than the more granular information collected in a clinical trial, hence excluding cause of death in this analysis, which could be be a potential source of bias. Also, in OptumLabs, there is no reliable way to adjudicate paroxysmal versus persistent AF given the reliance on diagnosis codes. Therefore, we have not analyzed the AF type.

Third, the findings are reflective of insured patients in the United States. The generalizability to uninsured patients and those not in Medicare Advantage are uncertain.

Last, within administrative claims databases such as OptumLabs it is challenging to accurately ascertain arrhythmia outcomes and quality of life because in routine practice not all patients are regularly monitored. Therefore, in contrast to EAST-AFNET 4, we have not assessed the efficacy of rhythm-control therapy, the severity of AF symptoms, or the quality of life.

| Subgroup | Control | Early Rhythm Control | Hazard Ratio (95% CI) | P for interaction |
|---|---|---|---|---|
| | No. of patients/n of events/Person-Years/Event Rate per 100 person-years | | | |
| **Age** | | | | 0.026 |
| <75 years | 42869/84/1135/7.39 | 17483/62/1186/5.22 | 0.71 (0.57, 0.88) | |
| 75+ years | 39764/144/914/15.77 | 9623/133/879/15.16 | 0.96 (0.82, 1.14) | |
| **Sex** | | | | 0.789 |
| Female | 41368/99/824/11.97 | 11049/83/834/9.96 | 0.83 (0.68, 1.01) | |
| Male | 41265/129/1225/10.56 | 16057/112/1232/9.11 | 0.86 (0.73, 1.03) | |
| **Race** | | | | 0.543 |
| Asian/Black/Hispanic/Unknown | 19140/55/407/13.63 | 5116/47/443/10.69 | 0.79 (0.61, 1.03) | |
| White | 63493/173/1642/10.51 | 21990/148/1622/9.11 | 0.87 (0.75, 1.01) | |
| **$CHA_2DS_2$-VASc** | | | | 0.508 |
| 0-1 | 5173/2/157/1.43 | 2724/1/170/0.44 | 0.31 (0.05, 2.00) | |
| 2-3 | 17768/11/458/2.34 | 7153/10/442/2.25 | 0.97 (0.57, 1.64) | |
| 4+ | 59692/215/1435/14.98 | 17229/185/1454/12.72 | 0.85 (0.74, 0.97) | |
| **Left ventricular hypertrophy** | | | | 0.277 |
| No | 54884/103/1268/8.10 | 16063/94/1263/7.42 | 0.92 (0.75, 1.11) | |
| Yes | 27749/125/781/16.04 | 11043/101/802/12.65 | 0.80 (0.67, 0.95) | |
| **Systolic heart failure** | | | | 0.987 |
| No | 68661/131/1637/8.02 | 20996/106/1602/6.60 | 0.83 (0.69, 0.98) | |
| Yes | 13972/97/412/23.47 | 6110/89/463/19.32 | 0.83 (0.68, 1.01) | |
| **Cardiomyopathy** | | | | <0.001 |
| No | 66463/145/1445/10.03 | 20301/104/1493/6.95 | 0.69 (0.59, 0.82) | |
| Yes | 16170/83/605/13.75 | 6805/91/572/15.97 | 1.16 (0.94, 1.43) | |
| **Obstructive sleep apnea** | | | | 0.803 |
| No | 64736/168/1523/11.01 | 19314/145/1534/9.44 | 0.86 (0.74, 1.00) | |
| Yes | 17897/60/527/11.47 | 7792/50/531/9.47 | 0.82 (0.63, 1.06) | |
| **Thromboembolism** | | | | 0.457 |
| No | 61012/139/1572/8.86 | 21508/125/1589/7.84 | 0.89 (0.75, 1.05) | |
| Yes | 21621/89/477/18.60 | 5598/71/476/14.83 | 0.80 (0.65, 0.99) | |

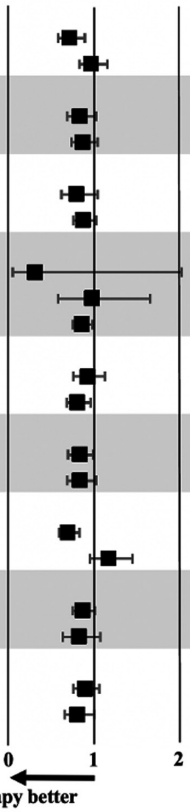



**Figure 3. Subgroup analysis for the primary outcome in propensity score–weighted patients.**
Hazard ratios and *P* values for interaction are based on Cox proportional hazards regression analyses on the composite end point of all-cause mortality, stroke, or hospitalization with the diagnoses of heart failure or myocardial infarction. There were significant interactions between early rhythm control and age, as well as cardiomyopathy, which imply that the reduction in the composite end point associated with early rhythm control was greater in patients aged <75 years and patients without cardiomyopathy.

## CONCLUSIONS

In this large routine-care data set, three quarters of patients with new-onset AF would be eligible for early rhythm control as tested in EAST-AFNET 4. ERC was associated with lower rates of a composite of stroke, death, and hospitalization for HF or MI. Our data support the routine initiation of ERC as part of the management of patients with recently diagnosed AF.

## ARTICLE INFORMATION

Received November 19, 2021; accepted March 8, 2022.

### Affiliations

Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN (J.D., P.A.F., D.L.P., P.A.N., X.Y.); Department of Cardiology, University Heart and Vascular Center Hamburg, University Hospital Hamburg Eppendorf, Hamburg, Germany (J.D., P.K., L.H.D.); DZHK (German Center for Cardiovascular Research), Partner Site Hamburg/Kiel/Lübeck, Berlin, Germany (J.D., P.K.); Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, United Kingdom (P.K.); OptumLabs, Eden Prairie, MN (H.K.V.H., L.R.S.); and Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, MN (H.K.V.H., L.R.S., P.A.N., X.Y.).

### Sources of Funding

Dr Dickow was supported by the German Heart Foundation (S/06/19; Mit Fördermitteln der Deutsche Herzstiftung e.V.). Dr Kirchhof is partially supported by European Union BigData@Heart (grant agreement EU IMI 116074), British Heart Foundation (FS/13/43/30324; PG/17/30/32961 and PG/20/22/35093; AA/18/2/34218), German Centre for Cardiovascular Research supported by the German Ministry of Education and Research (DZHK), and Leducq Foundation. Dr Packer is funded in part by a Clinician Investigator award from the Mayo Foundation. Dr Noseworthy receives research funding from the National Institutes of Health, including the National Heart, Lung, and Blood Institute (R21AG 62580–1, R01HL 131535-4, R01HL 143070-2), the National Institute on Aging (R01AG 062436-1), the Agency for Healthcare Research and Quality (R01HS 25402-3), the Food and Drug Administration (FD 06292), and the American Heart Association (18SFRN34230146). Over the past 36 months, Dr Yao has received research support through Mayo Clinic from the National Institutes of Health (R21HL140205, R01AG062436), the Agency for Healthcare Research and Quality (R01HS025402), the Food and Drug Administration (U01FD005938), the University of Nebraska Medical Center, and the Medical Devices Innovation Consortium/National Evaluation System for health Technology.

### Disclosures

Dr Kirchhof receives research support for basic, translational, and clinical research projects from European Union, British Heart Foundation, Leducq Foundation, Medical Research Council (UK), and the German Centre for Cardiovascular Research, from several drug and device companies active in AF, and has received honoraria from several such companies in the past but not in the past 3 years. Dr Kirchhof is listed as inventor on 2 patents held by University of Birmingham (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783). Dr Packer in the past 12 months has provided consulting services for Abbott; AtriFix; Biosense Webster, Inc.; Cardio Syntax; EBAmed; Johnson & Johnson $0; MediaSphere Medical; LLC<$5000; MedLumics; Medtronic; NeuCures; St. Jude Medical; Siemens; Spectrum Dynamics; Centrix; and Thermedical. Dr Packer received no personal compensation for these consulting activities, unless noted. Dr Packer receives research funding from Abbott; Biosense Webster; Boston Scientific/EPT; CardioInsight; EBAmed; German Heart Foundation; Medtronic; National Institutes of Health; Robertson Foundation; St. Jude Medical; Siemens; Thermedical; Inc.; Vital Project Funds, Inc.; and Mr. and Mrs. J. Michael Cook. Dr Packer and Mayo Clinic jointly have equity in a privately held company, External Beam Ablation Medical Devices. Royalties from Wiley & Sons, Oxford, and St Jude Medical. Dr Noseworthy is a study investigator in an ablation trial sponsored by Medtronic. Dr Noseworthy and Mayo Clinic are involved in potential equity/royalty relationship with AliveCor. Dr Noseworthy has served on an expert advisory panel for Optum. Dr Noseworthy and Mayo Clinic have filed patents related to the application of artificial intelligence to the ECG for diagnosis and risk stratification. All other authors have nothing to declare.

### Supplemental Material

Data S1
Tables S1–S17

## REFERENCES

1. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*. 1998;98:946–952. doi: 10.1161/01.CIR.98.10.946
2. Friberg L, Hammar N, Pettersson H, Rosenqvist M. Increased mortality in paroxysmal atrial fibrillation: report from the Stockholm Cohort-Study of Atrial Fibrillation (SCAF). *Eur Heart J*. 2007;28:2346–2353. doi: 10.1093/eurheartj/ehm308
3. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, Said SA, Darmanata JI, Timmermans AJM, Tijssen JGP, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med*. 2002;347:1834–1840. doi: 10.1056/NEJMoa021375
4. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002;347:1825–1833. doi: 10.1056/NEJMoa021328
5. Carlsson J, Miketic S, Windeler J, Cuneo A, Haun S, Micus S, Walter S, Tebbe U. Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the strategies of treatment of atrial fibrillation (STAF) study. *J Am Coll Cardiol*. 2003;41:1690–1696. doi: 10.1016/S0735-1097(03)00332-2
6. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, Bourassa MG, Arnold JMO, Buxton AE, Camm AJ, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med*. 2008;358:2667–2677. doi: 10.1056/NEJMoa0708789
7. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, Fetsch T, van Gelder IC, Haase D, Haegeli LM, et al. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med*. 2020;383:1305–1316. doi: 10.1056/NEJMoa2019422
8. Kirchhof P, Bax J, Blomstrom-Lundquist C, Calkins H, Camm AJ, Cappato R, Cosio F, Crijns H, Diener H-C, Goette A, et al. Early and comprehensive management of atrial fibrillation: executive summary of the proceedings from the 2nd AFNET-EHRA consensus conference "research perspectives in AF". *Eur Heart J*. 2009;30:2969–2980. doi: 10.1093/eurheartj/ehp235
9. Kirchhof P. Can we improve outcomes in AF patients by early therapy? *BMC Med*. 2009;7:72. doi: 10.1186/1741-7015-7-72
10. Wallace PJ, Shah ND, Dennen T, Bleicher PA, Crown WH. Optum labs: building a novel node in the learning health care system. *Health Aff*. 2014;33:1187–1194. doi: 10.1377/hlthaff.2014.0038
11. Optum Research Data Assets. Available at https://www.optum.com/content/dam/optum/resources/productSheets/5302_Data_Assets_Chart_Sheet_ISPOR.pdf. Accessed October 17, 2020.
12. Noseworthy PA, Gersh BJ, Kent DM, Piccini JP, Packer DL, Shah ND, Yao X. Atrial fibrillation ablation in practice: assessing CABANA generalizability. *Eur Heart J*. 2019;40:1257–1264. doi: 10.1093/eurheartj/ehz085
13. Noseworthy PA, Van Houten HK, Gersh BJ, Packer DL, Friedman PA, Shah ND, Dunlay SM, Siontis KC, Piccini JP, Yao X. Generalizability of the CASTLE-AF trial: catheter ablation for patients with atrial fibrillation and heart failure in routine practice. *Heart Rhythm*. 2020;17:1057–1065. doi: 10.1016/j.hrthm.2020.02.030
14. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28:3083–3107. doi: 10.1002/sim.3697
15. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496. doi: 10.1080/01621459.1999.10474144
16. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994;81:515–526. doi: 10.1093/biomet/81.3.515
17. Cosedis Nielsen J, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Kongstad O, Pehrson S, Englund A, Hartikainen J,

Mortensen LS, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. *N Engl J Med*. 2012;367:1587–1595. doi: 10.1056/NEJMoa1113566
18. Andrade JG, Wells GA, Deyell MW, Bennett M, Essebag V, Champagne J, Roux J-F, Yung D, Skanes A, Khaykin Y, et al. Cryoablation or drug therapy for initial treatment of atrial fibrillation. *N Engl J Med*. 2021;384:305–315. doi: 10.1056/NEJMoa2029980
19. Wazni OM, Dandamudi G, Sood N, Hoyt R, Tyler J, Durrani S, Niebauer M, Makati K, Halperin B, Gauri A, et al. Cryoballoon ablation as initial therapy for atrial fibrillation. *N Engl J Med*. 2021;384:316–324. doi: 10.1056/NEJMoa2029554
20. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Poole JE, Noseworthy PA, Rosenberg YD, Jeffries N, Mitchell LB, et al. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA*. 2019;321:1261–1274. doi: 10.1001/jama.2019.0693
21. Kim D, Yang P-S, You SC, Sung J-H, Jang E, Yu HT, Kim T-H, Pak H-N, Lee M-H, Lip GYH, et al. Treatment timing and the effects of rhythm control strategy in patients with atrial fibrillation: nationwide cohort study. *BMJ*. 2021;373:n991. doi: 10.1136/bmj.n991
22. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan G-A, Dilaveris PE, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2021;42:373–498. doi: 10.1093/eurheartj/ehaa612
23. Andrade JG, Verma A, Mitchell LB, Parkash R, Leblanc K, Atzema C, Healey JS, Bell A, Cairns J, Connolly S, et al. 2018 Focused update of the canadian cardiovascular society guidelines for the management of atrial fibrillation. *Can J Cardiol*. 2018;34:1371–1392. doi: 10.1016/j.cjca.2018.08.026
24. Kumamaru H, Judd SE, Curtis JR, Ramachandran R, Hardy NC, Rhodes JD, Safford MM, Kissela BM, Howard G, Jalbert JJ, et al. Validity of claims-based stroke algorithms in contemporary medicare data: reasons for geographic and racial differences in stroke (REGARDS) study linked with medicare claims. *Circ Cardiovasc Qual Outcomes*. 2014;7:611–619. doi: 10.1161/CIRCOUTCOMES.113.000743
25. Kokotailo RA, Hill MD. Coding of stroke and stroke risk factors using International Classification of Diseases, revisions 9 and 10. *Stroke*. 2005;36:1776–1781. doi: 10.1161/01.STR.0000174293.17959.a1
26. Fan J, Arruda-Olson AM, Leibson CL, Smith C, Liu G, Bailey KR, Kullo IJ. Billing code algorithms to identify cases of peripheral artery disease from administrative data. *J Am Med Informatics Assoc*. 2013;20:e349–e354. doi: 10.1136/amiajnl-2013-001827
27. Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA. Non-vitamin K antagonist oral anticoagulant dosing in patients with atrial fibrillation and renal dysfunction. *J Am Coll Cardiol*. 2017;69:2779–2790. doi: 10.1016/j.jacc.2017.03.600
28. Yao X, Tangri N, Gersh BJ, Sangaralingham LR, Shah ND, Nath KA, Noseworthy PA. Renal outcomes in anticoagulated patients with atrial fibrillation. *J Am Coll Cardiol*. 2017;70:2621–2632. doi: 10.1016/j.jacc.2017.09.1087

# SUPPLEMENTAL MATERIAL

# DATA S1. STATISTICAL ANALYSIS PLAN

The purpose of this analysis plan is to provide guide to our analyst when conducting the study. Most of the content will be included in the manuscript in order to guide researchers who want to replicate our findings or conduct similar studies. We also provided justifications for our methods and decisions so other researchers can make a choice or adjust their methods accordingly.

**ABBREVIATIONS**

| | |
|---|---|
| AAD | anti-arrhythmic drugs |
| AF | Atrial fibrillation |
| CI | Confidence interval |
| HR | Hazard ratio |
| IQR | Interquartile range |

**Key Definition**

**First AF Date** (variable name first_AF_date)

The date of the first AF diagnosis within the study period.

**Index Date** (variable name index_date)

The date 12 months after the first AF date and start of the follow up period.

**Baseline Period** (variable name baseline)

Time (≥12 months) before the first AF date, used to establish a patient's medical history, and to exclude prior AF diagnosis.

**Study Period**

The study population will be patients who were newly diagnosed with AF between 7/28/2011-12/30/2016, which is the enrollment period of the EAST trial, but patients were followed up until 12/31/2019.

**Early Rhythm Control Therapy**

The study aimed to compare patients treated with early rhythm control therapy (AF ablation and/or AADs), here defined as within the first year of AF diagnosis, and those treated with usual care (rate control drugs). Some patients may be treated with both AF ablation and AADs.

## BACKGROUND AND OBJECTIVES

Atrial fibrillation (AF) imposes an increased risk for cardiovascular complications such as death, stroke and myocardial infarction, particularly in the first year after diagnosis.[1,2] Restoring and maintaining sinus rhythm is associated with reduced mortality.[3] Despite improved efficacy and safety of rhythm control therapy, previous trials have failed to demonstrate superiority over rate control.[4–6] However, rhythm control therapy appears to be more effective when applied early.[7,8]

Recently, the Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4) randomized patients with early-onset AF and increased cardiovascular risk ($CHA_2DS_2$-VASc-Score $\geq 2$) to early rhythm control therapy or current guideline-based usual care.[9] In this trial, stopped for efficacy, early rhythm control was associated with a lower risk of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome.

To further assess the generalizability of the EAST-AFNET 4 trial in routine practice in a large cohort of US patients with AF, we assessed the proportion of patients who would have met trial eligibility and examined the association between early rhythm control and clinical outcomes, stratified by trial eligibility.

## STUDY DESIGN AND DATA SOURCE

We will conduct a retrospective cohort analysis using OptumLabs Data Warehouse, which contains over 160 million privately insured and Medicare Advantage enrollees of all ages and races from all 50 states.[10,11] In 2014, this amounted to 19% of all commercially insured and Medicare Advantage beneficiaries in the U.S.

## STUDY POPULATION

The study population will be adult patients (≥18 years) who were newly diagnosed with AF between 7/28/2011-12/30/2016, which is the enrollment period of the EAST trial.

The study population will include two treatment groups: early rhythm control therapy (EAST) group and usual group. The EAST group will include patients who underwent early rhythm control therapy, i.e. AF ablation and/or any AAD therapy, within the first year after AF diagnosis. Some patients may be treated with both AF ablation and AAD. The usual care group will include patients who did not undergo early rhythm control therapy within the first year after AF diagnosis.

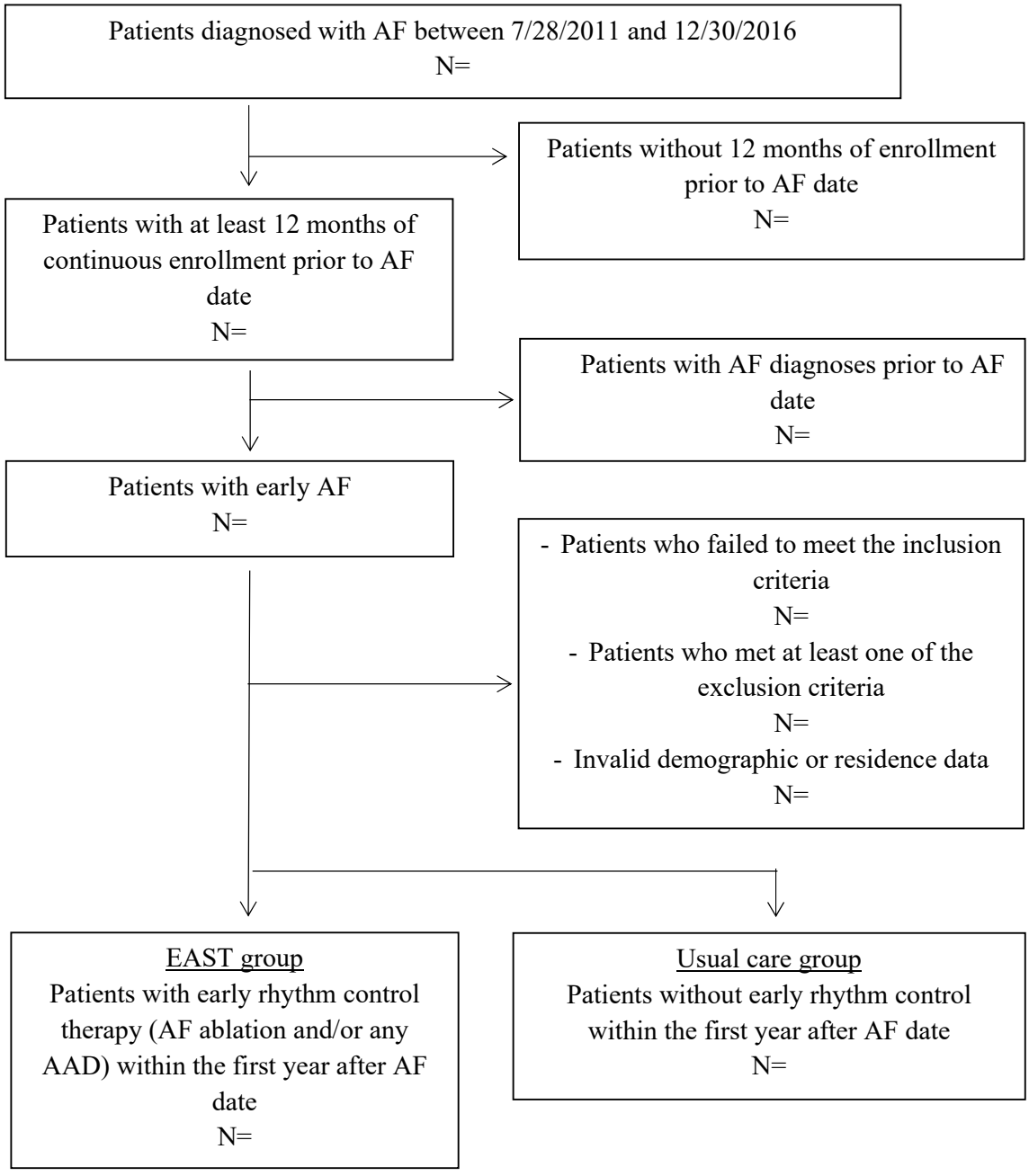
We will then limit to those who were older than 75 years of age or had had a previous transient ischemic attack or stroke, or met two of the following criteria: age greater than 65 years, female sex, heart failure, hypertension, diabetes mellitus, severe coronary artery disease, chronic kidney disease (Modification of Diet in Renal Disease stage 3 or 4 [glomerular filtration rate, 15 to 59 ml per minute per 1.73 m2 of body-surface area]), and left ventricular hypertrophy (diastolic septal wall width, >15 mm).

**Table 1. Generic Names of Anti-Arrhythmic Drug Therapy**

| | | **Generic Names** |
|---|---|---|
| **Anti-arrhythmic drugs** | | amiodarone, dofetilide, dronedarone, flecainide, propafenone, sotalol, quinidine, disopyramide, moricizine, procainamide, azimilide |
| **Rate control drugs** | Beta Blockers | atenolol, bisoprolol, carvedilol, metoprolol, nadolol, nebivolol, propranolol, labetalol |
| | Calcium Blockers | diltiazem, verapamil |
| | Cardiac glycosides | digoxin, digitoxin |

Patients will be required to have at least 12 months of continuous enrollment in health insurance plans (both medical and prescription drug plans) before the index date, in order to capture an adequate prior medical history and to exclude AF diagnoses prior to the first AF date. Also, Patients were required to have AF diagnosis on at least two different days. Patients whose demographic or residence data are invalid will be excluded. We anticipate that few patients will be under 18 years, but if any patient is under 18 years, they will be excluded as well. We will need to fill out the flow diagram on the next page.

**Figure 1. Patients Selection Flow Diagram**



## MEASUREMENTS

### Baseline Characteristics

Baseline characteristics include socio-demographic characteristics, medical history, concurrent medication use, and previous treatment with rate control drugs. Socio-demographic characteristics include age, sex, race/ethnicity, and region, determined at the time of index date. Race/ethnicity is provided by OptumLabs, classified as non-Hispanic White (White), non-Hispanic Black (Black), Asian, Hispanic, or other/unknown. Self-report was the primary source, and when it was missing, imputation was made by the data provider based on other available administrative data.[12]

Medical history will be determined using patients' physician, facility and pharmacy claims before the index date. We will use all data available to us to establish patients' medical history, and the length of baseline period will be included in the propensity score model to avoid any potential bias. In our previous studies, the baseline period was on average 3-4 years, and there was no substantial difference in the length of the baseline period among different treatment groups, especially after propensity score matching or weighting.

Concurrent medication, such as anti-hypertensive and anti-diabetic medications, will be captured within 3 months of the index date. Previous treatment with rhythm or rate control drugs will be captured during the entire baseline, in the form of the number of previous AADs and the number of previous rate control drugs. Although patients with longer baseline period are more likely to have a larger number of previous drugs, the baseline period will not differ between treatment groups, and thus, this should not introduce any undue bias when comparing early rhythm control and usual care patients.

**Follow up and Outcomes**

OptumLabs Data Warehouse is continuously updated on a monthly basis and the data are complete within 6 months of the service being provided. To avoid potential interaction of the current COVID-19 pandemic with the outcomes, patients will be followed until December 31st, 2019, the end of enrollment in health insurance plans, or death, whichever happened first.

The primary outcomes will be a composite endpoint of all-cause mortality, stroke, or hospitalization with the diagnoses heart failure or acute coronary syndrome, and second, the number of nights spent in the hospital per year, i.e. the same primary endpoints as the EAST trial. The secondary outcomes will include each of these outcomes considered separately.

Mortality will be identified based on the Social Security Death Master File and discharge status. Before November 2011, the Social Security Death Master File has complete mortality data. However, effective on November 1st, 2011, Section 205(r) of the Social Security Act prohibits the Social Security Administration (SSA) from disclosing state death records that SSA receives through its contracts with the states, except in limited circumstances. Thus, if the SSA knows of a death only from the states and not from any of its other sources of death information, which happens roughly one-third of the time, those death data will not appear on the Death Master File.[13] Using discharge status (i.e. in-hospital death), we typically capture an additional 30% of deaths in addition to what has been captured by Death Master File. Therefore, most of the deaths missing from Death Master File should be captured by discharge status, particularly since most deaths occur in an institutional setting. We acknowledge that a small proportion of patients who died out of hospital and were not captured by Death Master File could be missing, however, this should be non-differential between treatment groups and should not influence our comparison. In fact, the mortality data is more reliable than most measures derived from administrative data, since its specificity is nearly perfect, and the sensitivity is also very high.

**Missing Data**

Studies using administrative claims data generally do not have the problem of missing data, *per se*. We will define the presence of a condition, outcome or drug use by the presence of a claim with eligible diagnosis or procedure codes or prescription fills. Patients will be considered to have a comorbidity, outcome or drug exposure if they have a claim, and will be considered not having a comorbidity, outcome or drug exposure if they do not have a claim. Therefore, we do not have missing data in comorbidities, drug use, or outcomes. However, misclassification may exist. This is a limitation of using claims data, but the algorithms used to define our outcomes of interest and important covariates are commonly used and have demonstrated good performance in previous studies.[14–18] Our internal validation also suggested good performance of the algorithms. We anticipate that any existing residual misclassification will be non-differential between treatment groups and should not meaningfully impact our findings.

For the demographic data, we typically will delete a very small percentage (<1%) of patients with invalid demographic data during the cohort creation process (e.g., missing residence region or inconsistent birth year). For race/ethnicity, the categories in the database are non-Hispanic white, non-Hispanic black, Hispanic, Asian, other and unknown. The other and unknown will be used as a separate category in the propensity score model.

**Internal Validation of Diagnosis Codes**

The codes and algorithms used herein have been commonly used and validated in many previous studies.[14–22]

We also leveraged the ability to link to laboratory results and electronic health records to validate our diagnosis codes. For example, we compared the ejection fraction documented in electronic health records and the diagnosis codes for HF. Using a cutoff of LVEF ≤40% for

heart failure with reduced ejection fraction (HFrEF) diagnosis codes and LVEF ≥50% for heart failure with preserved ejection fraction (HFpEF) codes, we observed the specificity of 91% and 81%, respectively, and sensitivity of 81% and 91%, respectively.

We also compared eGFR with the presence of a diagnosis code of Stage 3-4 chronic kidney disease (CKD) in those who did not have renal failure. We found 88% of patients who had a diagnosis of Stage 3-4 CKD had eGFR <60 mL/min/1.73m$^2$, and 90% of those who did not have a diagnosis had eGFR ≥60 mL/min/1.73m$^2$, which indicates good performance of the diagnosis codes. Moreover, the discrepancy between the diagnosis codes and eGFR could be because some patients may have a temporary decline in eGFR, but later recovered and did not develop to CKD or some patients had serum creatinine tests in facilities that did not submit data to the OptumLabs Data Warehouse.

We have also conducted validation of the major bleeding diagnosis codes based on the International Society on Thrombosis and Haemostasis (ISTH) criteria[23]: (1) fatal bleeding, and/or, (2) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or, (3) bleeding causing a fall in hemoglobin level of 2 g/dL or more, or leading to transfusion of two or more units of whole blood or red cells. We used ICD-9 and CPT procedure codes to identify transfusion, but we were not able to know the units of whole blood or red cells used in the transfusion. We also identified other procedures to control or manage bleeding, such as endoscopic procedures to address gastrointestinal bleeding, neurosurgical decompression for intracranial bleeding, evacuation of hematoma, or vascular embolization procedures to control bleeding. Among all bleeding events, one in four was bleeding in critical areas, and one third required transfusion. This is generally consistent with previous studies that adapted ISTH definition using administrative data.[24] Nearly 80% of patients had a procedure to control or manage bleeding. In patients with hemoglobin test results, we abstracted the most

recent test performed within six months prior to the bleeding. The median time from the previous hemoglobin test to the date of bleeding is 29 (IQR 8-66) days. The median hemoglobin level during the bleeding was 8.2 (IQR 7.3-11.2) g/dL, with a median drop of 2.1 (IQR 1.1-3.6) g/dL. Among patients with transfusion, the median hemoglobin level was 7.3 (IQR 6.5-8.1) g/dL with a median drop of 2.7 (IQR 1.1-3.6) g/dL. In patients without transfusion, the median hemoglobin level was 10.4 (IQR 8.2-12.3) g/dL, with a median drop of 2.1 (IQR 1.2-3.6) g/dL. Overall, 95% of patients identified using diagnosis codes had bleeding in critical area, or a transfusion, or a procedure used to control bleeding, which suggests high specificity of our algorithm. Even in the remaining 5% patients, the hemoglobin level was low, a median of 10.5 (IQR 8.7-12.0), with a median drop of 2.1 (IQR 1.2-3.5) g/dL.

## STATISTICAL METHODS

### Main Analyses

We will calculate the proportion of patients who would be excluded from the trial based on the operational definition below (Table 2). We will divide patients to three subgroups: (1) patients who would be eligible for EAST; (2) patients who failed to meet the inclusion criterion, i.e. those under 75 years without any stroke risk factors; (3) patients who met at least one of the exclusion criteria. Some patients may have both failed to meet the inclusion criterion and met the exclusion criteria. In the stratified analyses for clinical outcomes, such patients will be classified as those who met the exclusion criteria.

**Table 2: Proportion of patients meeting each of the EAST trial inclusion/exclusion criteria.**

| EAST Eligibility Criteria | Operational Definition in OLDW |
|---|---|
| **Inclusion criteria** | |
| Recent-onset AF (≤1 year before enrollment), here defined as early AF | AF diagnosis in study period without prior AF diagnosis in baseline period of at least 12 months |
| Age ≥18 years | Age ≥18 years |
| One of the following: Age >75 years, prior stroke or transient ischemic attack<br><br>Or 2 of the following: Age >65 years, female sex, arterial hypertension, diabetes mellitus, severe coronary artery disease (previous myocardial infarction, CABG, PCI), heart failure, left ventricular hypertrophy, chronic kidney disease (MDRD stage III or IV), peripheral artery disease | Age >75 years, diagnosis codes for stroke or transient ischemic attack<br><br>Age >65 years, female sex, diagnosis codes for arterial hypertension, diabetes mellitus, severe coronary artery disease (previous myocardial infarction, CABG, PCI), heart failure, left ventricular hypertrophy, chronic kidney disease (MDRD stage III or IV), peripheral artery disease |
| **Exclusion criteria** | |
| E1 Any disease that limits life expectancy to <1 year | See note below the table |
| E2 Participation in another clinical trial | - |
| E3 Previous participation in EAST | - |
| E4 Women of childbearing potential (unless post-menopausal or surgically sterile) | Women age <45 years |

| | |
|---|---|
| E5 Breastfeeding women | Women age <45 years |
| E6 Drug abuse | Procedure codes for drug abuse |
| E7 Prior AF ablation or surgical therapy for AF | AF diagnosis prior to index date; Procedure codes for maze procedure |
| E8 Previous therapy failure on amiodaron, eg, patients who had symptomatic recurrent AF that required escalation of therapy while on amiodarone | AF diagnosis prior to index date |
| E9 Patients not suitable for rhythm control of AF | See note below the table |
| E10 Severe mitral valve stenosis | Diagnosis codes for severe mitral valve stenosis |
| E11 Prosthetic mitral valve | Diagnosis codes for prosthetic mitral valve surgery |
| E12 Clinically relevant hepatic dysfunction requiring specific therapy | Diagnosis codes for hepatic dysfunction |
| E13 Clinically manifest thyroid dysfunction requiring therapy. After successful treatment of thyroid dysfunction, patients may be enrolled when their thyroid function is controlled. | Diagnosis codes for thyroid dysfunction |
| E14 Severe renal dysfunction (stage V, requiring or almost requiring dialysis) | Procedure codes for dialysis and diagnosis codes for renal dysfunction, stage V |

Note: Two EAST enrollment criteria could not be considered due to lack of availability in our dataset: medical conditions limiting expected survival to <1 year and contraindications for rhythm control therapy

AAD denotes anti-arrhythmic drug, AF atrial fibrillation, CABG coronary artery bypass graft, MI myocardial infarction, PCI percutaneous coronary intervention.

We will use propensity score overlap weighting to account for the differences in baseline characteristics between patients who underwent early rhythm control therapy and those who were treated with usual care (See the next section 5.2). Standardized mean difference will used to assess the balance of covariates after weighting and a difference less than 0.1 will be considered acceptable.[25]

Cox proportional hazards regression will be used to compare patients treated with early rhythm control therapy and patients treated with usual care in the propensity-score weighted cohort, with a robust sandwich estimator for variance estimation. The regression will be

performed in the overall cohort as well as in each of the three subgroups. The Fine and Gray method will be used to consider death as a competing risk when assessing non-fatal outcomes (i.e., stroke, bleeding, or cardiac arrest when considered separately).[26] The proportional hazards assumption will be tested on the basis of Schoenfeld residuals.[27] If the proportional hazards assumption does not hold, the hazard ratios will be interpreted as average effects over the observed times, and we will provide the cumulative risks and hazard ratios at different time points to facilitate the interpretation of the effects over time.[28,29]

A *P* value less than 0.05 will considered statistically significant for all tests. All tests will be 2-sided. All analyses will be conducted using SAS Enterprise Guide 7.1 (SAS Institute Inc.) and Stata 16.0 (Stata Corp).

**Propensity Score Methods**

A propensity score, the probability of undergoing early rhythm control therapy, will be estimated using logistic regression based on socio-demographics, medical history, concurrent medication use, the year of the index date, and the length of baseline period. We will use the overlap weight method to balance treatment groups. The overlap weight will be calculated as 1 minus propensity score for the early rhythm control therapy patients, and the propensity score for the usual care-treated patients. The propensity score and weight will be calculated in each of the three subgroups (patients who were eligible for EAST, patients who fail to meet the inclusion criteria, and patients who meet one of the exclusion criteria) in order to ensure optimal balance in each of the subgroups.

Other commonly used propensity score methods include propensity score matching and inverse probability treatment weighting (IPTW). We will not use propensity score matching as the main method because a large amount of patients may be dropped during matching, however, we will perform a sensitivity analysis using propensity score matching. We will not use IPTW,

since IPTW gave imprecise estimates of treatment effect and undue influence to a small number of observations when substantial confounding was present.[30] The performance of IPTW often gets worse when the prevalence of treatment is low.[31]

We chose the overlap weight because this approach minimizes the asymptotic variance of the treatment effect, while also possessing a desirable exact balance property.[32] Unlike IPTW, the overlap weights are bounded between 0 and 1 and thus are less sensitive to extreme weights. Compared to the common practice of truncating weights or discarding patients with extreme weights, the overlap weights avoid this arbitrary choice of a cutoff point for inclusion. The overlap weight also possesses an attractive exact balance property, i.e., the means of all variables (including the proportions of a binary or categorical variable) will be exactly the same between treatment and control groups after weighting.

The results using the overlap weight should be interpreted as the average treatment effect for the overlap population. The overlap population typically represents a target population of intrinsic substantive interest, i.e. patients who could appear in either treatment groups. In such patients, clinical consensus regarding the treatment choice is often ambiguous and thus research is most needed to guide decision making.

**Sensitivity Analyses**

We will conduct a few sensitivity analyses to assess the robustness of the findings. First, propensity score matching will be used instead of propensity score weighting for the primary outcome. One-to-one nearest neighborhood caliper matching will be used to match patients based on the logit of the propensity score using a caliper equal to 0.2 of the standard deviation of the logit of the propensity score.[33] Patients will be exact matched on whether they were eligible for the trial, failed to meet the inclusion criterion, or met at least one of the exclusion criteria.

Second, we will conduct a stratified analysis based on whether the early rhythm control-treated patients were treated with AF ablation or without AF ablation. To conduct the stratified analysis, we will first recalculate the propensity score weights to balance patients treated with early rhythm control and patients treated with usual care, and perform regression analyses to compare early rhythm control to usual care; we will then recalculate the weights to balance patients treated with AF ablation and patients treated with usual care, and perform regression analyses to compare AF ablation to usual care. Some of the early rhythm control-treated patients may have been treated with both AADs and AF ablation, and such patients will be classified to the ablation group.

Third, a similar stratified analysis will be conducted based on the adherence to AADs in the early rhythm control-treated patients, i.e., patients with proportion of days covered (PDC)<80% and those with PDC≥80%, since the adherence to AAD therapy in practice is often lower than that in clinical trials. The adherence will consider all rhythm control drugs that a patient used during follow up, even if they were different from the initial treatment. To conduct the stratified analysis, we will first recalculate the propensity score weights to balance patients who were treated with AADs and adherent and patients who were treated with usual care, and perform regression analyses to compare usual care-treated patients to adherent AAD-treated patients; we will then recalculate the weights to balance patients who were treated with usual care and patients who were treated with AADs and not adherent, and perform regression analyses to compare usual care-treated patients to non-adherent AAD-treated patients.

**Subgroup Analyses**

We will perform subgroup analyses for the primary outcome stratified by age, sex, race, $CHA_2DS_2$-VASc, hypertension with left ventricular hypertrophy, heart failure, cardiomyopathy, sleep apnea, and prior thromboembolism. The subgroup analyses will be performed separately in patients who were eligible for the trial, patients who failed to meet the

trial inclusion criterion, and patients who met at least one of the trial exclusion criteria. Patients who failed the trial inclusion criterion are those under 75 years without stroke risk factors, therefore, we will perform subgroup analyses only by sex and race.

Since an increasing number of subgroup analyses could increase the chance of false positive results, we pre-specified the above subgroups since they are either key demographic characteristics or risk factors strongly associated with the primary outcome. The subgroup analyses will not only explore whether there is any heterogeneity in treatment effects, but also help understand whether there is any subgroup of patients who may benefit from ablation but were not adequately represented in the trial.

For all analyses performed in this study, we will not perform any adjustment for multiple testing. The sample size will be large and thus even with the conservative Bonferroni adjustment, many tests will still be statistically significant. We will consider all the analyses except those related to the primary outcome exploratory. However, if the exploratory results, e.g., treatment heterogeneity in certain subgroups, are consistent with the EAST trial or are confirmed by future studies, the results will more likely to be a true finding.

**Residual Confounding**

We will assess falsification endpoints to test for residual confounding. Treatment effects estimated in observational studies are prone to unmeasured confounding. In recent years, falsification end point, also called control outcome, has become a popular method to assess for unmeasured confounding.[34–36] A falsification endpoint is a health outcome that researchers believe is highly unlikely to be casually related to the treatment in question. If a significant relationship is found between the treatment and a falsification endpoint, it may indicate the treatment groups are different in some unmeasured ways, i.e. the existence of unmeasured confounding. This method is similar to a negative control, a routine precaution taken in the

design of biologic laboratory experiments, and is recommended to be used to detect confounding and bias in observational studies.[35,37,38] We selected three endpoints that that are unlikely to be a result of undergoing early-rhythm control therapy – emergency room visit or hospitalization related to chronic obstructive pulmonary disease (COPD), pneumonia, and fracture.

## LIMITATIONS

Our study relies on administrative data to ascertain baseline characteristics and outcomes, which could be subject to misclassification. However, it is unlikely there is any systematic difference in the ascertainment of comorbidities and outcomes between different treatment groups, and thus, the misclassification should not meaningfully impact our comparisons between drugs. The diagnosis and procedure codes used in this study have been commonly used in previous studies, and demonstrated good performance in our internal validation using linked laboratory results and electronic health records (described in Section 4.4) as well as other validation studies with positive predictive value around 90%.[14,39–42]

Second, our study will only include privately insured and Medicare Advantage patients. The patient characteristics and outcomes could be different in the Medicaid, Medicare Fee-for-Service, and uninsured populations. However, the insurance coverage rates are high in older Americans. Over 90% of Americans aged 50-64 have health insurance and over 75% had private health insurance.[43] One in three Medicare patients is enrolled in Medicare Advantage.[44] Although traditionally Medicare Advantage attracted healthier people, after the risk adjustment system was phased in from 2004-2007, the favorable risk selection has been largely reduced.[45]

In fact, the results from this study will be more generalizable than most observational studies using other data sources. Observational studies largely use either administrative data or registries. Some cardiovascular registries focused on cardiology practices for recruitment and patients have to sign informed consent and agree to participate and to be actively followed, and thus the patients in these registries were more selective. Some administrative data are limited within a health system, within a region, or within an age range (e.g., Medicare, Kaiser, etc.). The OptumLabs Data Warehouse contains patients of all ages and races managed at heterogeneous practice settings from all 50 states.[10,11] The distribution of patient characteristics (e.g., age, sex and race/ethnicity) in the database is similar to those of the general U.S.

population.[11] The data are updated monthly and are generally believed to be timely, accurate, and reflective of contemporary practice patterns. The concordance between OptumLabs and everyday practice is a major strength of the data source.

**References**


1. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: The Framingham Heart Study. *Circulation*. 1998;98(10):946-952. doi:10.1161/01.CIR.98.10.946

2. Friberg L, Hammar N, Pettersson H, Rosenqvist M. Increased mortality in paroxysmal atrial fibrillation: Report from the Stockholm Cohort-Study of Atrial Fibrillation (SCAF). *Eur Heart J*. 2007;28(19):2346-2353. doi:10.1093/eurheartj/ehm308

3. Van Gelder IC, Hagens VE, Bosker HA, et al. A Comparison of Rate Control and Rhythm Control in Patients with Recurrent Persistent Atrial Fibrillation. *N Engl J Med*. 2002;347(23):1834-1840. doi:10.1056/NEJMoa021375

4. Wyse DG, Waldo AL, DiMarco JP, et al. A Comparison of Rate Control and Rhythm Control in Patients with Atrial Fibrillation. *N Engl J Med*. 2002;347(23):1825-1833. doi:10.1056/NEJMoa021328

5. Carlsson J, Miketic S, Windeler J, et al. Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: The strategies of treatment of atrial fibrillation (STAF) study. *J Am Coll Cardiol*. 2003;41(10):1690-1696. doi:10.1016/S0735-1097(03)00332-2

6. Roy D, Talajic M, Nattel S, et al. Rhythm Control versus Rate Control for Atrial Fibrillation and Heart Failure. *N Engl J Med*. 2008;358(25):2667-2677. doi:10.1056/NEJMoa0708789

7. Kirchhof P, Bax J, Blomstrom-Lundquist C, et al. Early and comprehensive management of atrial fibrillation: Executive summary of the proceedings from the 2nd AFNET-EHRA consensus conference "research perspectives in AF." *Eur Heart J*.

2009;30(24):2969-2980. doi:10.1093/eurheartj/ehp235

8. Kirchhof P. Can we improve outcomes in AF patients by early therapy? *BMC Med*. 2009;7(1):72. doi:10.1186/1741-7015-7-72

9. Kirchhof P, Camm AJ, Goette A, et al. Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. *N Engl J Med*. 2020;383(14):1305-1316. doi:10.1056/nejmoa2019422

10. Wallace PJ, Shah ND, Dennen T, Bleicher PA, Crown WH. Optum labs: Building a novel node in the learning health care system. *Health Aff*. 2014;33(7):1187-1194. doi:10.1377/hlthaff.2014.0038

11. *Optum Research Data Assets*. https://www.optum.com/content/dam/optum/resources/productSheets/5302_Data_Assets_Chart_Sheet_ISPOR.pdf. Accessed October 17, 2020.

12. Hershman DL, Tsui J, Wright JD, Coromilas EJ, Tsai WY, Neugut AI. Household net worth, racial disparities, and hormonal therapy adherence among women with early-stage breast cancer. *J Clin Oncol*. 2015;33(9):1053-1059. doi:10.1200/JCO.2014.58.3062

13. Da Graca B, Filardo G, Nicewander D. Consequences for healthcare quality and research of the exclusion of records from the death master file. *Circ Cardiovasc Qual Outcomes*. 2013;6(1):124-128. doi:10.1161/CIRCOUTCOMES.112.968826

14. Tirschwell DL, Longstreth WT. Validating administrative data in stroke research. *Stroke*. 2002;33(10):2465-2470. doi:10.1161/01.STR.0000032240.28636.BD

15. Cunningham A, Stein CM, Chung CP, Daugherty JR, Smalley WE, Ray WA. An automated database case definition for serious bleeding related to oral anticoagulant

use. *Pharmacoepidemiol Drug Saf*. 2011;20(6):560-566. doi:10.1002/pds.2109

16. Arnason T, Wells PS, van Walraven C, Forster AJ. Accuracy of coding for possible warfarin complications in hospital discharge abstracts. *Thromb Res*. 2006;118(2):253-262. doi:10.1016/j.thromres.2005.06.015

17. Hwang YJ, Shariff SZ, Gandhi S, et al. Validity of the International Classification of Diseases, Tenth Revision code for acute kidney injury in elderly patients at presentation to the emergency department and at hospital admission. *BMJ Open*. 2012;2(6). doi:10.1136/bmjopen-2012-001821

18. Wilchesky M, Tamblyn RM, Huang A. Validation of diagnostic codes within medical services claims. *J Clin Epidemiol*. 2004;57(2):131-141. doi:10.1016/S0895-4356(03)00246-4

19. Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA. Non–Vitamin K Antagonist Oral Anticoagulant Dosing in Patients With Atrial Fibrillation and Renal Dysfunction. *J Am Coll Cardiol*. 2017;69(23):2779-2790. doi:10.1016/j.jacc.2017.03.600

20. Yao X, Tangri N, Gersh BJ, et al. Renal Outcomes in Anticoagulated Patients With Atrial Fibrillation. *J Am Coll Cardiol*. 2017;70(21):2621-2632. doi:10.1016/j.jacc.2017.09.1087

21. Noseworthy PA, Gersh BJ, Kent DM, et al. Atrial fibrillation ablation in practice: Assessing CABANA generalizability. *Eur Heart J*. 2019;40(16):1257-1264. doi:10.1093/eurheartj/ehz085

22. Noseworthy PA, Van Houten HK, Gersh BJ, et al. Generalizability of the CASTLE-AF trial: Catheter ablation for patients with atrial fibrillation and heart failure in routine

practice. *Hear Rhythm*. 2020;17(7):1057-1065. doi:10.1016/j.hrthm.2020.02.030

23. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3(4):692-694. doi:10.1111/j.1538-7836.2005.01204.x

24. Jasuja GK, Reisman JI, Miller DR, et al. Identifying major hemorrhage with automated data: Results of the Veterans Affairs Study to Improve Anticoagulation (VARIA). *Thromb Res*. 2013;131(1):31-36. doi:10.1016/j.thromres.2012.10.010

25. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28(25):3083-3107. doi:10.1002/sim.3697

26. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *J Am Stat Assoc*. 1999;94(446):496. doi:10.2307/2670170

27. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994;81(3):515-526. doi:10.1093/biomet/81.3.515

28. Therneau TM, Grambsch PM. *Modeling Survival Data: Extending the Cox Model*. New York, NY: Springer New York; 2000. doi:10.1007/978-1-4757-3294-8

29. Weintraub WS, Grau-Sepulveda M V., Weiss JM, et al. Comparative effectiveness of revascularization strategies. *N Engl J Med*. 2012;366(16):1467-1476. doi:10.1056/NEJMoa1110717

30. Elze MC, Gregson J, Baber U, et al. Comparison of Propensity Score Methods and Covariate Adjustment: Evaluation in 4 Cardiovascular Studies. *J Am Coll Cardiol*. 2017;69(3):345-357. doi:10.1016/j.jacc.2016.10.060

31. Austin PC, Schuster T. The performance of different propensity score methods for

estimating absolute effects of treatments on survival outcomes: A simulation study. *Stat Methods Med Res*. 2016;25(5):2214-2237. doi:10.1177/0962280213519716

32. Li F, Morgan KL, Zaslavsky AM. Balancing Covariates via Propensity Score Weighting. *J Am Stat Assoc*. 2018;113(521):390-400. doi:10.1080/01621459.2016.1260466

33. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat*. 2011;10(2):150-161. doi:10.1002/pst.433

34. Prasad V, Jena AB. Prespecified falsification end points: Can they validate true observational associations? *JAMA - J Am Med Assoc*. 2013;309(3):241-242. doi:10.1001/jama.2012.96867

35. Dusetzina SB, Brookhart MA, MacIejewski ML. Control outcomes and exposures for improving internal validity of nonrandomized studies. *Health Serv Res*. 2015;50(5):1432-1451. doi:10.1111/1475-6773.12279

36. Ioannidis JPA. Are mortality differences detected by administrative data reliable and actionable? *JAMA - J Am Med Assoc*. 2013;309(13):1410-1411. doi:10.1001/jama.2013.3150

37. Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative Controls: A tool for detecting confounding and bias in observational studies. *Epidemiology*. 2010;21(3):383-388. doi:10.1097/EDE.0b013e3181d61eeb

38. Wimmer NJ, Resnic FS, Mauri L, Matheny ME, Yeh RW. Comparison of transradial versus transfemoral percutaneous coronary intervention in routine practice: Evidence for the importance of “falsification hypotheses” in observational studies of comparative

effectiveness. *J Am Coll Cardiol*. 2013;62(22):2147-2148. doi:10.1016/j.jacc.2013.07.036

39. Kumamaru H, Judd SE, Curtis JR, et al. Validity of claims-based stroke algorithms in contemporary medicare data: Reasons for geographic and racial differences in stroke (REGARDS) study linked with medicare claims. *Circ Cardiovasc Qual Outcomes*. 2014;7(4):611-619. doi:10.1161/CIRCOUTCOMES.113.000743

40. Kokotailo RA, Hill MD. Coding of stroke and stroke risk factors using International Classification of Diseases, revisions 9 and 10. *Stroke*. 2005;36(8):1776-1781. doi:10.1161/01.STR.0000174293.17959.a1

41. Jensen PN, Johnson K, Floyd J, Heckbert SR, Carnahan R, Dublin S. A systematic review of validated methods for identifying atrial fibrillation using administrative data. *Pharmacoepidemiol Drug Saf*. 2012;21(SUPPL. 1):141-147. doi:10.1002/pds.2317

42. Fan J, Arruda-Olson AM, Leibson CL, et al. Billing code algorithms to identify cases of peripheral artery disease from administrative data. *J Am Med Informatics Assoc*. 2013;20(E2). doi:10.1136/amiajnl-2013-001827

43. Barnett J, Vornovitsky M. Health Insurance Coverage in the United States: 2015 - Current Population Reports. *28th Annu Data Users Conf Ref Doc*. September 2016. https://digitalcommons.unomaha.edu/datausers_reference_2017/4. Accessed October 17, 2020.

44. Medicare Advantage 2016 Spotlight: Enrollment Market Update | KFF. https://www.kff.org/medicare/issue-brief/medicare-advantage-2016-spotlight-enrollment-market-update/. Accessed October 17, 2020.

45. McWilliams JM, Hsu J, Newhouse JP. New risk-adjustment system was associated

with reduced favorable selection in medicare advantage. *Health Aff*. 2012;31(12):2630-2640. doi:10.1377/hlthaff.2011.1344

**Table S1. List of Rhythm- and Rate-Control Drugs**

| | | Generic Names |
|---|---|---|
| **Rhythm-control drugs** | | amiodarone, dofetilide, dronedarone, flecainide, propafenone, sotalol, quinidine, disopyramide, moricizine, procainamide, azimilide |
| **Rate-control drugs** | Beta Blockers | atenolol, bisoprolol, carvedilol, metoprol, nadolol, nebivolol, propranolol, labetalol |
| | Calcium Blockers | diltiazem, verapamil |
| | Cardiac glycosides | digoxin, digitoxin |

**Table S2. Diagnosis and Procedure Codes Used to Identify Key Conditions, Procedures, and Outcomes**

| | Diagnosis Codes | | Procedure Codes | | |
|---|---|---|---|---|---|
| | **ICD-9-CM** | **ICD-10-CM** | **CPT** | **ICD-9** | **ICD-10** |
| **Atrial Fibrillation** | 427.31 | I48.0, I48.1, I48.2, I48.91 | | | |
| **Catheter Ablation** | | | 93651, 93656, 93657 | 37.34 | 025S3ZZ, 025T3ZZ |
| **Ischemic stroke** | 433.x1, 434.x1, 436 | I63.x | | | |
| **Major bleeding** | | | | | |
| Gastrointestinal bleeding | 456.0, 456.20, 530.21, 530.7, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 537.83, 537.84, 562.02, 562.03, 562.12, 562.13, 569.3, 569.85, 578.x | I85.01, I85.11, K22.11,K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6 ,K27.0, K27.2, K27.4, K27.6, K28.0, K28.4, K28.6, K29.x1, K31.811, K31.82, K55.21, K57.x1, K57.x3, K62.5, K63.81, , K92.0, K92.1, K92.2, | | | |
| Intracranial bleeding | 430, 431, 432.x, 852.x, 853.x, 800.2x, 800.3x, 800.7x, 800.8x, 801.2x, 801.3x, 801.7x, 801.8x, 803.2x, 803.3x, 803.7x, 803.8x, 804.2x, 804.3x, 804.7x, 804.8x, | I60.x, I61.x, S06.34x, S06.35x, S06.36x, S06.37x, S06.38x, S06.4x, S06.5x, S06.6x | | | |
| Other bleeding | 423.0, 459.0, 568.81, 596.7, 599.71, 719.1x, 784.8, 786.3 | I31.2, K66.1, M25.0, R04.1, R04.2, R31.0, R58 | | | |
| **Cardiac arrest** | 427.5 | I46.x , I46.2, I46.8, I46.9 | | | |

ICD-9-CM denotes International Classification of Diseases, 9th Revision, Clinical Modification, ICD-10-CM International Classification of Diseases, 10th Revision, Clinical Modification, and CPT current procedural terminology.

**Table S3. EAST-AFNET 4 Trial Eligibility Criteria**

| EAST Eligibility Criteria | Operational Definition in OLDW |
|---|---|
| **Inclusion criteria** | |
| Recent-onset AF (≤1 year before enrollment), here defined as early AF | AF diagnosis in study period without prior AF diagnosis in baseline period of at least 12 months |
| Age ≥18 years | Age ≥18 years |
| One of the following: Age >75 years, prior stroke or transient ischemic attack<br><br>Or 2 of the following: Age >65 years, female sex, arterial hypertension, diabetes mellitus, severe coronary artery disease (previous myocardial infarction, CABG, PCI), heart failure, left ventricular hypertrophy, chronic kidney disease (MDRD stage III or IV), peripheral artery disease | Age >75 years, diagnosis codes for stroke or transient ischemic attack<br><br>Age >65 years, female sex, diagnosis codes for arterial hypertension, diabetes mellitus, severe coronary artery disease (previous myocardial infarction, CABG, PCI), heart failure, left ventricular hypertrophy, chronic kidney disease (MDRD stage III or IV), peripheral artery disease |
| **Exclusion criteria** | |
| E1 Any disease that limits life expectancy to <1 year | See note below the table |
| E2 Participation in another clinical trial | - |
| E3 Previous participation in EAST | - |
| E4 Women of childbearing potential (unless post-menopausal or surgically sterile) | Women age <45 years |
| E5 Breastfeeding women | Women age <45 years |
| E6 Drug abuse | Procedure codes for drug abuse |

**Table S3. EAST-AFNET 4 Trial Eligibility Criteria**

| | |
|---|---|
| E7 Prior AF ablation or surgical therapy for AF | AF diagnosis prior to index date; Procedure codes for maze procedure |
| E8 Previous therapy failure on amiodaron, eg, patients who had symptomatic recurrent AF that required escalation of therapy while on amiodarone | AF diagnosis prior to index date |
| E9 Patients not suitable for rhythm control of AF | See note below the table |
| E10 Severe mitral valve stenosis | Diagnosis codes for severe mitral valve stenosis |
| E11 Prosthetic mitral valve | Diagnosis codes for prosthetic mitral valve surgery |
| E12 Clinically relevant hepatic dysfunction requiring specific therapy | Diagnosis codes for hepatic dysfunction |
| E13 Clinically manifest thyroid dysfunction requiring therapy. After successful treatment of thyroid dysfunction, patients may be enrolled when their thyroid function is controlled. | Diagnosis codes for thyroid dysfunction |
| E14 Severe renal dysfunction (stage V, requiring or almost requiring dialysis) | Procedure codes for dialysis and diagnosis codes for renal dysfunction, stage V |

Note: Two EAST enrollment criteria could not be considered due to lack of availability in our dataset: medical conditions limiting expected survival to <1 year and contraindications for rhythm control therapy

AAD denotes anti-arrhythmic drug, AF atrial fibrillation, CABG coronary artery bypass graft, MI myocardial infarction, PCI percutaneous coronary intervention.

**Table S4. Baseline Characteristics Before and After PS Weighting in the Overall Cohort**

| | Before PS Weighting | | | After PS Weighting | | |
|---|---|---|---|---|---|---|
| | **Control (N=82,633)** | **Early Rhythm-Control (N=27,106)** | **Standardized Difference** | **Control (N=82,633)** | **Early Rhythm-Control (N=27,106)** | **Standardized Difference** |
| **Trial Eligibility** | | | | | | |
| Eligible | 61641 (74.6%) | 18307 (67.5%) | 0.156 | 70.6% | 70.6% | 0.000 |
| Ineligible | 20992 (25.4%) | 8799 (32.5%) | 0.156 | 29.4% | 29.4% | 0.000 |
| **Age** | | | | | | |
| Mean (SD) | 71.7 (11.6) | 68.9 (11.4) | 0.245 | 70.1 (12.3) | 70.1 (11.9) | 0.000 |
| **Age group** | | | | | | |
| 18-64 years | 20226 (24.5%) | 9103 (33.6%) | 0.202 | 29.9% | 29.9% | 0.000 |
| 65-74 years | 22643 (27.4%) | 8380 (30.9%) | 0.077 | 26.5% | 26.5% | 0.000 |
| 75+ years | 39764 (48.1%) | 9623 (35.5%) | 0.258 | 43.6% | 43.6% | 0.000 |
| **Female** | 41368 (50.1%) | 11049 (40.8%) | 0.188 | 40.3% | 40.3% | 0.000 |
| **Race** | | | | | | |
| Asian | 2059 (2.5%) | 552 (2.0%) | 0.031 | 2.7% | 2.7% | 0.000 |
| Black | 9646 (11.7%) | 2395 (8.8%) | 0.094 | 10.2% | 10.2% | 0.000 |
| Hispanic | 5436 (6.6%) | 1510 (5.6%) | 0.042 | 7.0% | 7.0% | 0.000 |
| Unknown | 1999 (2.4%) | 659 (2.4%) | 0.001 | 2.2% | 2.2% | 0.000 |
| White | 63493 (76.8%) | 21990 (81.1%) | 0.105 | 77.9% | 77.9% | 0.000 |
| **Region** | | | | | | |

**Table S4. Baseline Characteristics Before and After PS Weighting in the Overall Cohort**

| | | | | | | |
|---|---|---|---|---|---|---|
| Midwest | 24462 (29.6%) | 8702 (32.1%) | 0.054 | 29.3% | 29.3% | 0.000 |
| Northeast | 17587 (21.3%) | 3255 (12.0%) | 0.251 | 18.0% | 18.0% | 0.000 |
| South | 32477 (39.3%) | 11972 (44.2%) | 0.099 | 41.6% | 41.6% | 0.000 |
| Unknown | 59 (0.1%) | 34 (0.1%) | 0.017 | 0.0% | 0.0% | 0.000 |
| West | 8048 (9.7%) | 3143 (11.6%) | 0.060 | 11.0% | 11.0% | 0.000 |
| **Comorbidities** | | | | | | |
| Systolic HF | 13972 (16.9%) | 6110 (22.5%) | 0.142 | 25.7% | 25.7% | 0.000 |
| Cardiomyopathy | | | | | | |
| None | 66463 (80.4%) | 20301 (74.9%) | 0.133 | 68.9% | 68.9% | 0.000 |
| Hypertrophic | 1061 (1.3%) | 452 (1.7%) | 0.032 | 2.7% | 2.7% | 0.000 |
| Ischemic | 3836 (4.6%) | 1624 (6.0%) | 0.060 | 8.1% | 8.1% | 0.000 |
| Dilated | 11273 (13.6%) | 4729 (17.4%) | 0.105 | 20.3% | 20.3% | 0.000 |
| Implanted device | | | | | | |
| None | 71960 (87.1%) | 23112 (85.3%) | 0.053 | 75.1% | 75.1% | 0.000 |
| CRT defibrillator | 456 (0.6%) | 235 (0.9%) | 0.038 | 1.9% | 1.9% | 0.000 |
| ICD | 4301 (5.2%) | 1530 (5.6%) | 0.019 | 12.3% | 12.3% | 0.000 |
| CRT pacemaker | 73 (0.1%) | 26 (0.1%) | 0.002 | 0.3% | 0.3% | 0.000 |
| Dual chamber pacemaker | 4361 (5.3%) | 1589 (5.9%) | 0.025 | 7.5% | 7.5% | 0.000 |
| Single chamber pacemaker | 1482 (1.8%) | 614 (2.3%) | 0.033 | 3.0% | 3.0% | 0.000 |
| Indication for defibrillator | | | | | | |
| No defibrillator | 77876 (94.2%) | 25341 (93.5%) | 0.031 | 85.8% | 85.8% | 0.000 |

**Table S4. Baseline Characteristics Before and After PS Weighting in the Overall Cohort**

| | | | | | | |
|---|---|---|---|---|---|---|
| Primary | 3052 (3.7%) | 969 (3.6%) | 0.006 | 7.0% | 7.0% | 0.000 |
| Secondary | 1705 (2.1%) | 796 (2.9%) | 0.056 | 7.2% | 7.2% | 0.000 |
| Other supraventricular arrhythmia | 9110 (11.0%) | 3691 (13.6%) | 0.079 | 23.7% | 23.7% | 0.000 |
| Atrial flutter | 8142 (9.9%) | 7096 (26.2%) | 0.435 | 27.2% | 27.2% | 0.000 |
| Ventricular arrhythmia | 10137 (12.3%) | 4458 (16.4%) | 0.119 | 24.9% | 24.9% | 0.000 |
| Prior ablation for other arrhythmias | 1354 (1.6%) | 3328 (12.3%) | 0.428 | 31.1% | 31.1% | 0.000 |
| Cardioversion | 4882 (5.9%) | 8639 (31.9%) | 0.703 | 13.6% | 13.6% | 0.000 |
| Surgical ablation/Maze procedure | 26 (0.0%) | 117 (0.4%) | 0.083 | 0.4% | 0.4% | 0.000 |
| Hypertension | 77653 (94.0%) | 24588 (90.7%) | 0.123 | 92.2% | 92.2% | 0.000 |
| Diabetes mellitus | 35307 (42.7%) | 9957 (36.7%) | 0.123 | 44.3% | 44.3% | 0.000 |
| Thromboembolism | 21621 (26.2%) | 5598 (20.7%) | 0.130 | 25.4% | 25.4% | 0.000 |
| Stroke | 17349 (21.0%) | 4233 (15.6%) | 0.139 | 20.1% | 20.1% | 0.000 |
| Ischemic stroke | 15246 (18.5%) | 3611 (13.3%) | 0.141 | 18.0% | 18.0% | 0.000 |
| TIA | 11505 (13.9%) | 3060 (11.3%) | 0.079 | 13.1% | 13.1% | 0.000 |
| CAD | 51266 (62.0%) | 17747 (65.5%) | 0.071 | 74.9% | 74.9% | 0.000 |
| PAD | 16673 (20.2%) | 4081 (15.1%) | 0.135 | 20.3% | 20.3% | 0.000 |
| Vascular disease (CAD or PAD) | 54359 (65.8%) | 18330 (67.6%) | 0.039 | 76.4% | 76.4% | 0.000 |
| Myocardial infarction | 20458 (24.8%) | 7086 (26.1%) | 0.032 | 34.0% | 34.0% | 0.000 |
| CABG | 11755 (14.2%) | 6096 (22.5%) | 0.215 | 33.3% | 33.3% | 0.000 |
| PCI | 13593 (16.4%) | 4676 (17.3%) | 0.021 | 24.6% | 24.6% | 0.000 |
| Left ventricular hypertrophy | 27749 (33.6%) | 11043 (40.7%) | 0.149 | 41.3% | 41.3% | 0.000 |

**Table S4. Baseline Characteristics Before and After PS Weighting in the Overall Cohort**

| | | | | | | |
|---|---|---|---|---|---|---|
| Prior valve procedure | 2436 (2.9%) | 2577 (9.5%) | 0.274 | 6.4% | 6.4% | 0.000 |
| Mitral stenosis | 2114 (2.6%) | 991 (3.7%) | 0.063 | 4.4% | 4.4% | 0.000 |
| Mitral regurgitation | 33144 (40.1%) | 13692 (50.5%) | 0.210 | 49.1% | 49.1% | 0.000 |
| Major bleeding | 26015 (31.5%) | 8241 (30.4%) | 0.023 | 32.0% | 32.0% | 0.000 |
| Intracranial bleeding | 2995 (3.6%) | 785 (2.9%) | 0.041 | 3.2% | 3.2% | 0.000 |
| Stage 3-5 CKD | 16496 (20.0%) | 4683 (17.3%) | 0.069 | 20.4% | 20.4% | 0.000 |
| Renal failure requiring dialysis | 1558 (1.9%) | 414 (1.5%) | 0.028 | 1.6% | 1.6% | 0.000 |
| Liver disease | 14697 (17.8%) | 4674 (17.2%) | 0.014 | 18.0% | 18.0% | 0.000 |
| Non skin cancer | 18294 (22.1%) | 5494 (20.3%) | 0.046 | 20.2% | 20.2% | 0.000 |
| Fall | 19920 (24.1%) | 4991 (18.4%) | 0.139 | 22.1% | 22.1% | 0.000 |
| Anemia | 48170 (58.3%) | 15301 (56.4%) | 0.037 | 60.8% | 60.8% | 0.000 |
| Alcoholism | 5589 (6.8%) | 1771 (6.5%) | 0.009 | 5.9% | 5.9% | 0.000 |
| Smoking | 31269 (37.8%) | 11296 (41.7%) | 0.078 | 42.1% | 42.1% | 0.000 |
| Hypothyroidism | 27649 (33.5%) | 8569 (31.6%) | 0.039 | 34.9% | 34.9% | 0.000 |
| Thyrotoxicosis | 4734 (5.7%) | 1379 (5.1%) | 0.028 | 6.2% | 6.2% | 0.000 |
| Esophageal disease | 45830 (55.5%) | 14450 (53.3%) | 0.043 | 56.1% | 56.1% | 0.000 |
| Obesity | 27124 (32.8%) | 9998 (36.9%) | 0.085 | 35.4% | 35.4% | 0.000 |
| COPD | 20287 (24.6%) | 6224 (23.0%) | 0.037 | 25.5% | 25.5% | 0.000 |
| Obstructive sleep apnea | 17897 (21.7%) | 7792 (28.7%) | 0.164 | 27.4% | 27.4% | 0.000 |
| Hyperlipidemia | 72653 (87.9%) | 23596 (87.1%) | 0.026 | 89.6% | 89.6% | 0.000 |
| Osteoporosis | 18135 (21.9%) | 4700 (17.3%) | 0.116 | 17.9% | 17.9% | 0.000 |

**Table S4. Baseline Characteristics Before and After PS Weighting in the Overall Cohort**

| | | | | | | |
|---|---|---|---|---|---|---|
| Pneumonia | 23114 (28.0%) | 7322 (27.0%) | 0.021 | 30.8% | 30.8% | 0.000 |
| Fracture | 20148 (24.4%) | 5751 (21.2%) | 0.076 | 24.2% | 24.2% | 0.000 |
| Dementia | 11613 (14.1%) | 1876 (6.9%) | 0.234 | 11.7% | 11.7% | 0.000 |
| **Previous Drug Treatment** | | | | | | |
| N of previous AADs | | | | | | |
| 0 | 81963 (99.2%) | 525 (1.9%) | 8.365 | 31.2% | 31.2% | 0.000 |
| 1 | 654 (0.8%) | 24006 (88.6%) | 3.757 | 67.0% | 67.0% | 0.000 |
| 2+ | 16 (0.0%) | 2575 (9.5%) | 0.457 | 1.7% | 1.7% | 0.000 |
| Amiodarone use | 464 (0.6%) | 15908 (58.7%) | 1.651 | 47.5% | 47.5% | 0.000 |
| N of previous rate control drugs | | | | | | |
| 0 | * | * | 0.466 | 0.2% | 0.2% | 0.000 |
| 1 | 50530 (61.1%) | 13120 (48.4%) | 0.258 | 48.3% | 48.3% | 0.000 |
| 2 | 23494 (28.4%) | 7850 (29.0%) | 0.012 | 33.1% | 33.1% | 0.000 |
| 3+ | * | * | 0.075 | 18.3% | 18.3% | 0.000 |
| **Concurrent Medication** | | | | | | |
| Oral anticoagulants | | | | | | |
| none | 58496 (70.8%) | 15345 (56.6%) | 0.298 | 72.0% | 72.0% | 0.000 |
| Warfarin | 12247 (14.8%) | 4277 (15.8%) | 0.027 | 12.6% | 12.6% | 0.000 |
| NOAC | 11890 (14.4%) | 7484 (27.6%) | 0.329 | 15.4% | 15.4% | 0.000 |
| ACE inhibitors | 23343 (28.2%) | 7249 (26.7%) | 0.034 | 28.3% | 28.3% | 0.000 |
| ARB | 14396 (17.4%) | 4645 (17.1%) | 0.008 | 17.9% | 17.9% | 0.000 |

**Table S4. Baseline Characteristics Before and After PS Weighting in the Overall Cohort**

| | | | | | | |
|---|---|---|---|---|---|---|
| Thiazides | 14465 (17.5%) | 4016 (14.8%) | 0.073 | 13.5% | 13.5% | 0.000 |
| Beta blockers (rate control) | 57825 (70.0%) | 14417 (53.2%) | 0.350 | 67.2% | 67.2% | 0.000 |
| Other beta blockers (not rate control) | 4001 (4.8%) | 1051 (3.9%) | 0.047 | 3.8% | 3.8% | 0.000 |
| Calcium channel blockers (rate control) | 11854 (14.3%) | 2833 (10.5%) | 0.118 | 10.8% | 10.8% | 0.000 |
| Other calcium channel blockers (not rate control) | 14858 (18.0%) | 4059 (15.0%) | 0.081 | 14.8% | 14.8% | 0.000 |
| Digitalis | 5311 (6.4%) | 1174 (4.3%) | 0.093 | 6.9% | 6.9% | 0.000 |
| Diuretics--aldosterone antagonist | 4138 (5.0%) | 1481 (5.5%) | 0.020 | 5.9% | 5.9% | 0.000 |
| Loop diuretics | 19304 (23.4%) | 6551 (24.2%) | 0.019 | 27.1% | 27.1% | 0.000 |
| Other antihypertensive drugs | 7381 (8.9%) | 2026 (7.5%) | 0.053 | 7.7% | 7.7% | 0.000 |
| Statin | 40234 (48.7%) | 13081 (48.3%) | 0.009 | 52.1% | 52.1% | 0.000 |
| Insulin | 7308 (8.8%) | 1680 (6.2%) | 0.100 | 9.8% | 9.8% | 0.000 |
| Metformin | 10076 (12.2%) | 3014 (11.1%) | 0.033 | 11.6% | 11.6% | 0.000 |
| Other antidiabetic drugs | 9048 (10.9%) | 2452 (9.0%) | 0.063 | 9.7% | 9.7% | 0.000 |
| Antiplatelet | 10219 (12.4%) | 2532 (9.3%) | 0.097 | 13.4% | 13.4% | 0.000 |
| NSAIDs | 7411 (9.0%) | 2140 (7.9%) | 0.039 | 9.1% | 9.1% | 0.000 |
| Antiulcer agents | 22637 (27.4%) | 6819 (25.2%) | 0.051 | 26.7% | 26.7% | 0.000 |
| Antidepressant | 19648 (23.8%) | 4991 (18.4%) | 0.132 | 23.4% | 23.4% | 0.000 |
| **$CHA_2DS_2$-VASc** | | | | | | |
| Mean (SD) | 4.7 (2.0) | 4.3 (2.1) | 0.224 | 4.7 (2.1) | 4.7 (2.1) | 0.000 |
| **$CHA_2DS_2$-VASc group** | | | | | | |
| 0-1 | 5173 (6.3%) | 2724 (10.0%) | 0.139 | 7.4% | 7.4% | 0.000 |

**Table S4. Baseline Characteristics Before and After PS Weighting in the Overall Cohort**

| | | | | | | |
|---|---|---|---|---|---|---|
| 2-3 | 17768 (21.5%) | 7153 (26.4%) | 0.115 | 21.0% | 21.0% | 0.000 |
| 4+ | 59692 (72.2%) | 17229 (63.6%) | 0.187 | 71.7% | 71.7% | 0.000 |
| **Baseline period duration, years** | | | | | | |
| Mean (SD) | 4.9 (2.8) | 5.2 (3.0) | 0.104 | 5.1 (2.9) | 5.1 (2.9) | 0.000 |
| **Index year** | | | | | | |
| 2012 | 5216 (6.3%) | 1851 (6.8%) | 0.021 | 7.1% | 7.1% | 0.000 |
| 2013 | 14483 (17.5%) | 4940 (18.2%) | 0.018 | 15.3% | 15.3% | 0.000 |
| 2014 | 14168 (17.1%) | 4273 (15.8%) | 0.037 | 17.8% | 17.8% | 0.000 |
| 2015 | 13590 (16.4%) | 4417 (16.3%) | 0.004 | 17.2% | 17.2% | 0.000 |
| 2016 | 16629 (20.1%) | 5440 (20.1%) | 0.001 | 20.7% | 20.7% | 0.000 |
| 2017 | 18547 (22.4%) | 6185 (22.8%) | 0.009 | 21.9% | 21.9% | 0.000 |
| **Health Utilization within past 12 months** | | | | | | |
| Number of emergency room visits | | | | | | |
| Mean (SD) | 0.8 (1.5) | 0.8 (1.3) | 0.024 | 0.9 (1.7) | 0.9 (1.5) | 0.000 |
| Number of inpatient stays | | | | | | |
| Mean (SD) | 0.9 (1.2) | 1.2 (1.3) | 0.295 | 1.0 (1.5) | 1.0 (1.1) | 0.000 |
| Number of days in hospital | | | | | | |
| Mean (SD) | 5.9 (12.0) | 8.6 (13.3) | 0.212 | 6.5 (14.5) | 6.5 (10.0) | 0.000 |
| Number of HF hospitalizations | | | | | | |
| Mean (SD) | 0.1 (0.5) | 0.2 (0.6) | 0.121 | 0.2 (0.6) | 0.2 (0.5) | 0.000 |

## Table S4. Baseline Characteristics Before and After PS Weighting in the Overall Cohort

AAD denotes anti-arrhythmic drug, ACE angiotensin-converting enzyme, AF atrial fibrillation, ARB angiotensin II receptor blockers, CABG coronary artery bypass grafting, CAD coronary artery disease, CKD chronic kidney disease, COPD chronic obstructive pulmonary disease, CRT cardiac resynchronization therapy, HCM hypertrophic cardiomyopathy, ICD implantable cardioverter defibrillators, ILR implantable loop recorder, NSAID nonsteroidal anti-inflammatory drug, PAD peripheral artery disease, PCI percutaneous coronary intervention, PS propensity score, TIA transient ischemic attack.The $CHA_2DS_2$-VASc score is a 0- to 9-point stroke risk score where a higher point score indicates higher risk of stroke. The point score is calculated as follows: 1 point each for heart failure, hypertension, diabetes, vascular disease, age 65 to 74 years, and female sex and 2 points for age 75 years or older and prior thromboembolism (including ischemic stroke, TIA or systemic embolism).

Concurrent medication use was defined as prescriptions within three months prior to the index date.

* To maintain de-identification, OptumLabs does not allow researchers to disclose the number of events when the number is 10 or fewer.

**Table S5. Baseline Characteristics Before and After Propensity Score Weighting in Trial Eligible Patients**

| | Before PS Weighting | | | After PS Weighting | | |
|---|---|---|---|---|---|---|
| | **Control (N=61,641)** | **Early Rhythm-Control (N=18,307)** | **Standardized Difference** | **Control (N=61,641)** | **Early Rhythm-Control (N=18,307)** | **Standardized Difference** |
| **Age** | | | | | | |
| Mean (SD) | 73.8 (9.7) | 71.0 (9.9) | 0.281 | 72.5 (10.4) | 72.5 (9.8) | 0.000 |
| **Age group** | | | | | | |
| 18-64 years | 10769 (17.5%) | 4674 (25.5%) | 0.197 | 22.5% | 22.5% | 0.000 |
| 65-74 years | 17663 (28.7%) | 6201 (33.9%) | 0.113 | 28.0% | 28.0% | 0.000 |
| 75+ years | 33209 (53.9%) | 7432 (40.6%) | 0.268 | 49.5% | 49.5% | 0.000 |
| **Female** | 33223 (53.9%) | 8338 (45.5%) | 0.168 | 42.8% | 42.8% | 0.000 |
| **Race** | | | | | | |
| Asian | 1578 (2.6%) | 379 (2.1%) | 0.033 | 3.0% | 3.0% | 0.000 |
| Black | 6940 (11.3%) | 1599 (8.7%) | 0.084 | 9.5% | 9.5% | 0.000 |
| Hispanic | 3942 (6.4%) | 979 (5.3%) | 0.045 | 7.0% | 7.0% | 0.000 |
| Unknown | 1501 (2.4%) | 443 (2.4%) | 0.001 | 1.9% | 1.9% | 0.000 |
| White | 47680 (77.4%) | 14907 (81.4%) | 0.101 | 78.6% | 78.6% | 0.000 |
| **Region** | | | | | | |
| Midwest | 18431 (29.9%) | 5981 (32.7%) | 0.060 | 29.6% | 29.6% | 0.000 |
| Northeast | 13672 (22.2%) | 2193 (12.0%) | 0.274 | 19.4% | 19.4% | 0.000 |

**Table S5. Baseline Characteristics Before and After Propensity Score Weighting in Trial Eligible Patients**

| | | | | | | |
|---|---|---|---|---|---|---|
| South | 23813 (38.6%) | 8132 (44.4%) | 0.118 | 41.0% | 41.0% | 0.000 |
| Unknown | 36 (0.1%) | 15 (0.1%) | 0.009 | 0.1% | 0.1% | 0.000 |
| West | 5689 (9.2%) | 1986 (10.8%) | 0.054 | 9.9% | 9.9% | 0.000 |
| **Comorbidities** | | | | | | |
| Systolic HF | 9732 (15.8%) | 4045 (22.1%) | 0.161 | 23.5% | 23.5% | 0.000 |
| Cardiomyopathy | | | | | | |
| None | 50066 (81.2%) | 13649 (74.6%) | 0.161 | 68.7% | 68.7% | 0.000 |
| Hypertrophic | 742 (1.2%) | 284 (1.6%) | 0.030 | 2.5% | 2.5% | 0.000 |
| Ischemic | 2805 (4.6%) | 1111 (6.1%) | 0.068 | 8.0% | 8.0% | 0.000 |
| Dilated | 8028 (13.0%) | 3263 (17.8%) | 0.133 | 20.8% | 20.8% | 0.000 |
| Implanted device | | | | | | |
| None | 53654 (87.0%) | 15531 (84.8%) | 0.064 | 75.1% | 75.1% | 0.000 |
| CRT defibrillator | 316 (0.5%) | 165 (0.9%) | 0.046 | 1.4% | 1.4% | 0.000 |
| ICD | 3256 (5.3%) | 1074 (5.9%) | 0.025 | 12.5% | 12.5% | 0.000 |
| CRT pacemaker | 53 (0.1%) | 12 (0.1%) | 0.007 | 0.3% | 0.3% | 0.000 |
| Dual chamber pacemaker | 3335 (5.4%) | 1163 (6.4%) | 0.040 | 8.0% | 8.0% | 0.000 |
| Single chamber pacemaker | 1027 (1.7%) | 362 (2.0%) | 0.023 | 2.7% | 2.7% | 0.000 |
| Indication for defibrillator | | | | | | |
| No defibrillator | 58069 (94.2%) | 17068 (93.2%) | 0.040 | 86.1% | 86.1% | 0.000 |
| Primary | 2316 (3.8%) | 678 (3.7%) | 0.003 | 6.7% | 6.7% | 0.000 |
| Secondary | 1256 (2.0%) | 561 (3.1%) | 0.065 | 7.2% | 7.2% | 0.000 |

**Table S5. Baseline Characteristics Before and After Propensity Score Weighting in Trial Eligible Patients**

| | | | | | | |
|---|---|---|---|---|---|---|
| Other supraventricular arrhythmia | 6564 (10.6%) | 2475 (13.5%) | 0.088 | 22.4% | 22.4% | 0.000 |
| Atrial flutter | 5796 (9.4%) | 4709 (25.7%) | 0.439 | 25.2% | 25.2% | 0.000 |
| Ventricular arrhythmia | 7154 (11.6%) | 3009 (16.4%) | 0.139 | 24.6% | 24.6% | 0.000 |
| Prior ablation for other arrhythmias | 887 (1.4%) | 2105 (11.5%) | 0.418 | 29.0% | 29.0% | 0.000 |
| Cardioversion | 3442 (5.6%) | 6022 (32.9%) | 0.739 | 13.0% | 13.0% | 0.000 |
| Hypertension | 59693 (96.8%) | 17507 (95.6%) | 0.064 | 96.6% | 96.6% | 0.000 |
| Diabetes mellitus | 27188 (44.1%) | 7346 (40.1%) | 0.081 | 46.7% | 46.7% | 0.000 |
| Thromboembolism | 16185 (26.3%) | 3941 (21.5%) | 0.111 | 25.3% | 25.3% | 0.000 |
| Stroke | 12825 (20.8%) | 2953 (16.1%) | 0.121 | 19.8% | 19.8% | 0.000 |
| Ischemic stroke | 11343 (18.4%) | 2543 (13.9%) | 0.123 | 17.9% | 17.9% | 0.000 |
| TIA | 8688 (14.1%) | 2190 (12.0%) | 0.063 | 13.3% | 13.3% | 0.000 |
| CAD | 38692 (62.8%) | 12333 (67.4%) | 0.097 | 77.7% | 77.7% | 0.000 |
| PAD | 12239 (19.9%) | 2777 (15.2%) | 0.124 | 19.7% | 19.7% | 0.000 |
| Vascular disease (CAD or PAD) | 41221 (66.9%) | 12797 (69.9%) | 0.065 | 79.5% | 79.5% | 0.000 |
| Myocardial infarction | 15217 (24.7%) | 5102 (27.9%) | 0.072 | 34.3% | 34.3% | 0.000 |
| CABG | 8549 (13.9%) | 4029 (22.0%) | 0.213 | 34.1% | 34.1% | 0.000 |
| PCI | 10494 (17.0%) | 3453 (18.9%) | 0.048 | 25.6% | 25.6% | 0.000 |
| Left ventricular hypertrophy | 20241 (32.8%) | 7409 (40.5%) | 0.159 | 39.9% | 39.9% | 0.000 |
| Mitral regurgitation | 23987 (38.9%) | 8850 (48.3%) | 0.191 | 46.6% | 46.6% | 0.000 |
| Major bleeding | 18518 (30.0%) | 5483 (30.0%) | 0.002 | 30.0% | 30.0% | 0.000 |
| Intracranial bleeding | 2107 (3.4%) | 532 (2.9%) | 0.029 | 3.1% | 3.1% | 0.000 |

**Table S5. Baseline Characteristics Before and After Propensity Score Weighting in Trial Eligible Patients**

| | | | | | | |
|---|---|---|---|---|---|---|
| Stage 3-5 CKD | 11010 (17.9%) | 3013 (16.5%) | 0.037 | 19.2% | 19.2% | 0.000 |
| Liver disease | 9339 (15.2%) | 2937 (16.0%) | 0.025 | 16.4% | 16.4% | 0.000 |
| Non skin cancer | 13856 (22.5%) | 3948 (21.6%) | 0.022 | 21.1% | 21.1% | 0.000 |
| Fall | 14550 (23.6%) | 3442 (18.8%) | 0.118 | 22.3% | 22.3% | 0.000 |
| Anemia | 35129 (57.0%) | 10092 (55.1%) | 0.038 | 60.5% | 60.5% | 0.000 |
| Alcoholism | 355 (0.6%) | 88 (0.5%) | 0.013 | 0.4% | 0.4% | 0.000 |
| Smoking | 21773 (35.3%) | 7415 (40.5%) | 0.107 | 40.2% | 40.2% | 0.000 |
| Hypothyroidism | 21170 (34.3%) | 6158 (33.6%) | 0.015 | 36.6% | 36.6% | 0.000 |
| Thyrotoxicosis | 3468 (5.6%) | 963 (5.3%) | 0.016 | 6.6% | 6.6% | 0.000 |
| Esophageal disease | 33750 (54.8%) | 9884 (54.0%) | 0.015 | 55.5% | 55.5% | 0.000 |
| Obesity | 19821 (32.2%) | 7007 (38.3%) | 0.128 | 34.6% | 34.6% | 0.000 |
| COPD | 14404 (23.4%) | 4155 (22.7%) | 0.016 | 24.9% | 24.9% | 0.000 |
| Obstructive sleep apnea | 12574 (20.4%) | 5181 (28.3%) | 0.185 | 26.9% | 26.9% | 0.000 |
| Hyperlipidemia | 55492 (90.0%) | 16479 (90.0%) | 0.000 | 92.2% | 92.2% | 0.000 |
| Osteoporosis | 14462 (23.5%) | 3527 (19.3%) | 0.103 | 19.2% | 19.2% | 0.000 |
| Pneumonia | 16238 (26.3%) | 4884 (26.7%) | 0.008 | 28.7% | 28.7% | 0.000 |
| Fracture | 14546 (23.6%) | 3845 (21.0%) | 0.062 | 22.5% | 22.5% | 0.000 |
| Dementia | 8876 (14.4%) | 1318 (7.2%) | 0.234 | 12.1% | 12.1% | 0.000 |
| **Previous Drug Treatment** | | | | | | |
| N of previous AADs | | | | | | |
| 0 | 61152 (99.2%) | 308 (1.7%) | 8.827 | 29.1% | 29.1% | 0.000 |

**Table S5. Baseline Characteristics Before and After Propensity Score Weighting in Trial Eligible Patients**

| | | | | | | |
|---|---|---|---|---|---|---|
| 1 | 476 (0.8%) | 16152 (88.2%) | 3.704 | 68.9% | 68.9% | 0.000 |
| 2+ | 13 (0.0%) | 1847 (10.1%) | 0.472 | 2.0% | 2.0% | 0.000 |
| Amiodarone use | 340 (0.6%) | 10636 (58.1%) | 1.631 | 49.2% | 49.2% | 0.000 |
| N of previous rate control drugs | | | | | | |
| 0 | * | * | 0.455 | 0.2% | 0.2% | 0.000 |
| 1 | 38046 (61.7%) | 8785 (48.0%) | 0.279 | 46.8% | 46.8% | 0.000 |
| 2 | 17527 (28.4%) | 5398 (29.5%) | 0.023 | 34.5% | 34.5% | 0.000 |
| 3+ | * | * | 0.103 | 18.5% | 18.5% | 0.000 |
| **Concurrent Medication** | | | | | | |
| Oral anticoagulants | | | | | | |
| none | 42311 (68.6%) | 9687 (52.9%) | 0.326 | 70.2% | 70.2% | 0.000 |
| Warfarin | 9410 (15.3%) | 2818 (15.4%) | 0.004 | 12.5% | 12.5% | 0.000 |
| NOAC | 9920 (16.1%) | 5802 (31.7%) | 0.372 | 17.3% | 17.3% | 0.000 |
| ACE inhibitors | 18543 (30.1%) | 5292 (28.9%) | 0.026 | 30.0% | 30.0% | 0.000 |
| ARB | 11542 (18.7%) | 3575 (19.5%) | 0.020 | 20.6% | 20.6% | 0.000 |
| Thiazides | 11852 (19.2%) | 3062 (16.7%) | 0.065 | 14.9% | 14.9% | 0.000 |
| Beta blockers (rate control) | 44101 (71.5%) | 9835 (53.7%) | 0.375 | 69.8% | 69.8% | 0.000 |
| Other beta blockers (not rate control) | 2902 (4.7%) | 728 (4.0%) | 0.036 | 3.6% | 3.6% | 0.000 |
| Calcium channel blockers (rate control) | 9256 (15.0%) | 2032 (11.1%) | 0.116 | 11.5% | 11.5% | 0.000 |
| Other calcium channel blockers (not rate control) | 11391 (18.5%) | 2994 (16.4%) | 0.056 | 16.5% | 16.5% | 0.000 |

**Table S5. Baseline Characteristics Before and After Propensity Score Weighting in Trial Eligible Patients**

| | | | | | | |
|---|---|---|---|---|---|---|
| Digitalis | 4199 (6.8%) | 820 (4.5%) | 0.101 | 7.6% | 7.6% | 0.000 |
| Diuretics--aldosterone antagonist | 3059 (5.0%) | 1066 (5.8%) | 0.038 | 6.3% | 6.3% | 0.000 |
| Loop diuretics | 14263 (23.1%) | 4542 (24.8%) | 0.039 | 27.8% | 27.8% | 0.000 |
| Other antihypertensive drugs | 5314 (8.6%) | 1426 (7.8%) | 0.030 | 7.7% | 7.7% | 0.000 |
| Statin | 31464 (51.0%) | 9308 (50.8%) | 0.004 | 56.3% | 56.3% | 0.000 |
| Insulin | 5283 (8.6%) | 1190 (6.5%) | 0.078 | 10.2% | 10.2% | 0.000 |
| Metformin | 8504 (13.8%) | 2436 (13.3%) | 0.014 | 12.9% | 12.9% | 0.000 |
| Other antidiabetic drugs | 7312 (11.9%) | 1904 (10.4%) | 0.046 | 10.6% | 10.6% | 0.000 |
| Antiplatelet | 7978 (12.9%) | 1918 (10.5%) | 0.077 | 14.6% | 14.6% | 0.000 |
| NSAIDs | 5485 (8.9%) | 1439 (7.9%) | 0.037 | 9.3% | 9.3% | 0.000 |
| Antiulcer agents | 16766 (27.2%) | 4693 (25.6%) | 0.035 | 27.6% | 27.6% | 0.000 |
| Antidepressant | 14078 (22.8%) | 3276 (17.9%) | 0.123 | 22.3% | 22.3% | 0.000 |
| **$CHA_2DS_2$-VASc** | | | | | | |
| Mean (SD) | 4.9 (1.8) | 4.6 (1.8) | 0.203 | 5.0 (1.8) | 5.0 (1.8) | 0.000 |
| **$CHA_2DS_2$-VASc group** | | | | | | |
| 0-1 | 484 (0.8%) | 321 (1.8%) | 0.087 | 0.9% | 0.9% | 0.000 |
| 2-3 | 13728 (22.3%) | 5279 (28.8%) | 0.151 | 22.4% | 22.4% | 0.000 |
| 4+ | 47429 (76.9%) | 12707 (69.4%) | 0.171 | 76.7% | 76.7% | 0.000 |
| **Baseline period duration, years** | | | | | | |
| Mean (SD) | 4.8 (2.7) | 5.1 (2.9) | 0.108 | 5.0 (2.8) | 5.0 (2.8) | 0.000 |
| **Index year** | | | | | | |

**Table S5. Baseline Characteristics Before and After Propensity Score Weighting in Trial Eligible Patients**

| | | | | | | |
|---|---|---|---|---|---|---|
| 2012 | 3797 (6.2%) | 1241 (6.8%) | 0.025 | 6.7% | 6.7% | 0.000 |
| 2013 | 10756 (17.4%) | 3309 (18.1%) | 0.016 | 15.0% | 15.0% | 0.000 |
| 2014 | 10569 (17.1%) | 2848 (15.6%) | 0.043 | 17.3% | 17.3% | 0.000 |
| 2015 | 10110 (16.4%) | 2959 (16.2%) | 0.006 | 17.9% | 17.9% | 0.000 |
| 2016 | 12531 (20.3%) | 3679 (20.1%) | 0.006 | 21.2% | 21.2% | 0.000 |
| 2017 | 13878 (22.5%) | 4271 (23.3%) | 0.019 | 21.8% | 21.8% | 0.000 |
| **Health Utilization within past 12 months** | | | | | | |
| Number of emergency room visits | | | | | | |
| Mean (SD) | 0.7 (1.3) | 0.8 (1.2) | 0.068 | 0.8 (1.6) | 0.8 (1.3) | 0.000 |
| Number of inpatient stays | | | | | | |
| Mean (SD) | 0.8 (1.1) | 1.2 (1.2) | 0.370 | 0.9 (1.4) | 0.9 (1.0) | 0.000 |
| Number of days in hospital | | | | | | |
| Mean (SD) | 5.0 (10.2) | 7.9 (11.9) | 0.255 | 6.1 (14.1) | 6.1 (9.5) | 0.000 |
| Number of HF hospitalizations | | | | | | |
| Mean (SD) | 0.1 (0.4) | 0.2 (0.5) | 0.142 | 0.1 (0.5) | 0.1 (0.5) | 0.000 |

AAD denotes anti-arrhythmic drug, ACE angiotensin-converting enzyme, AF atrial fibrillation, ARB angiotensin II receptor blockers, CABG coronary artery bypass grafting, CAD coronary artery disease, CKD chronic kidney disease, COPD chronic obstructive pulmonary disease, CRT cardiac resynchronization therapy, HCM hypertrophic cardiomyopathy, ICD implantable cardioverter defibrillators, ILR implantable loop recorder, NSAID nonsteroidal anti-inflammatory drug, PAD peripheral artery disease, PCI percutaneous coronary intervention, PS propensity score, TIA transient ischemic attack.The $CHA_2DS_2$-VASc score is a 0- to 9-point stroke risk score where a higher point score indicates higher risk of stroke. The point score is calculated as follows: 1 point each for heart failure, hypertension, diabetes, vascular disease, age 65 to 74 years, and female sex and 2 points for age 75 years or older and prior thromboembolism (including ischemic stroke, TIA or systemic embolism). Concurrent medication use was defined as prescriptions within three months prior to the index date. * To maintain de-identification, OptumLabs does not allow researchers to disclose the number of events when the number is 10 or fewer.

**Table S6. Baseline Characteristics Before and After Propensity Score Weighting in Trial Ineligible Patients**

| | Before PS Weighting | | | After PS Weighting | | |
|---|---|---|---|---|---|---|
| | **Control (N=20,992)** | **Early Rhythm-Control (N=8799)** | **Standardized Difference** | **Control (N=20,992)** | **Early Rhythm-Control (N=8799)** | **Standardized Difference** |
| **Age** | | | | | | |
| Mean (SD) | 65.6 (14.1) | 64.4 (13.0) | 0.087 | 64.4 (14.5) | 64.4 (14.2) | 0.000 |
| **Age group** | | | | | | |
| 18-64 years | 9457 (45.1%) | 4429 (50.3%) | 0.106 | 47.6% | 47.6% | 0.000 |
| 65-74 years | 4980 (23.7%) | 2179 (24.8%) | 0.024 | 23.0% | 23.0% | 0.000 |
| 75+ years | 6555 (31.2%) | 2191 (24.9%) | 0.141 | 29.4% | 29.4% | 0.000 |
| **Female** | 8145 (38.8%) | 2711 (30.8%) | 0.168 | 34.4% | 34.4% | 0.000 |
| **Race** | | | | | | |
| Asian | 481 (2.3%) | 173 (2.0%) | 0.023 | 1.8% | 1.8% | 0.000 |
| Black | 2706 (12.9%) | 796 (9.0%) | 0.123 | 12.0% | 12.0% | 0.000 |
| Hispanic | 1494 (7.1%) | 531 (6.0%) | 0.044 | 6.8% | 6.8% | 0.000 |
| Unknown | 498 (2.4%) | 216 (2.5%) | 0.005 | 2.9% | 2.9% | 0.000 |
| White | 15813 (75.3%) | 7083 (80.5%) | 0.125 | 76.5% | 76.5% | 0.000 |
| **Region** | | | | | | |
| Midwest | 6031 (28.7%) | 2721 (30.9%) | 0.048 | 28.5% | 28.5% | 0.000 |
| Northeast | 3915 (18.6%) | 1062 (12.1%) | 0.183 | 14.7% | 14.7% | 0.000 |
| South | 8664 (41.3%) | 3840 (43.6%) | 0.048 | 43.0% | 43.0% | 0.000 |

**Table S6. Baseline Characteristics Before and After Propensity Score Weighting in Trial Ineligible Patients**

| | | | | | | |
|---|---|---|---|---|---|---|
| Unknown | 23 (0.1%) | 19 (0.2%) | 0.026 | 0.0% | 0.0% | 0.000 |
| West | 2359 (11.2%) | 1157 (13.1%) | 0.058 | 13.7% | 13.7% | 0.000 |
| **Comorbidities** | | | | | | |
| Systolic HF | 4240 (20.2%) | 2065 (23.5%) | 0.079 | 31.0% | 31.0% | 0.000 |
| Cardiomyopathy | | | | | | |
| None | 16397 (78.1%) | 6652 (75.6%) | 0.060 | 69.6% | 69.6% | 0.000 |
| Hypertrophic | 319 (1.5%) | 168 (1.9%) | 0.030 | 3.1% | 3.1% | 0.000 |
| Ischemic | 1031 (4.9%) | 513 (5.8%) | 0.041 | 8.3% | 8.3% | 0.000 |
| Dilated | 3245 (15.5%) | 1466 (16.7%) | 0.033 | 19.0% | 19.0% | 0.000 |
| Implanted device | | | | | | |
| None | 18306 (87.2%) | 7581 (86.2%) | 0.031 | 74.9% | 74.9% | 0.000 |
| CRT defibrillator | 140 (0.7%) | 70 (0.8%) | 0.015 | 3.0% | 3.0% | 0.000 |
| ICD | 1045 (5.0%) | 456 (5.2%) | 0.009 | 11.9% | 11.9% | 0.000 |
| CRT pacemaker | 20 (0.1%) | 14 (0.2%) | 0.018 | 0.3% | 0.3% | 0.000 |
| Dual chamber pacemaker | 1026 (4.9%) | 426 (4.8%) | 0.002 | 6.2% | 6.2% | 0.000 |
| Single chamber pacemaker | 455 (2.2%) | 252 (2.9%) | 0.044 | 3.8% | 3.8% | 0.000 |
| Indication for defibrillator | | | | | | |
| No defibrillator | 19807 (94.4%) | 8273 (94.0%) | 0.014 | 85.2% | 85.2% | 0.000 |
| Primary | 736 (3.5%) | 291 (3.3%) | 0.011 | 7.6% | 7.6% | 0.000 |
| Secondary | 449 (2.1%) | 235 (2.7%) | 0.035 | 7.3% | 7.3% | 0.000 |
| Other supraventricular arrhythmia | 2546 (12.1%) | 1216 (13.8%) | 0.050 | 26.8% | 26.8% | 0.000 |

**Table S6. Baseline Characteristics Before and After Propensity Score Weighting in Trial Ineligible Patients**

| | | | | | | |
|---|---|---|---|---|---|---|
| Atrial flutter | 2346 (11.2%) | 2387 (27.1%) | 0.414 | 31.8% | 31.8% | 0.000 |
| Ventricular arrhythmia | 2983 (14.2%) | 1449 (16.5%) | 0.063 | 25.7% | 25.7% | 0.000 |
| Prior ablation for other arrhythmias | 467 (2.2%) | 1223 (13.9%) | 0.439 | 36.1% | 36.1% | 0.000 |
| Cardioversion | 1440 (6.9%) | 2617 (29.7%) | 0.619 | 14.9% | 14.9% | 0.000 |
| Surgical ablation/Maze procedure | 26 (0.1%) | 117 (1.3%) | 0.142 | 1.3% | 1.3% | 0.000 |
| Hypertension | 17960 (85.6%) | 7081 (80.5%) | 0.136 | 81.8% | 81.8% | 0.000 |
| Diabetes mellitus | 8119 (38.7%) | 2611 (29.7%) | 0.191 | 38.6% | 38.6% | 0.000 |
| Thromboembolism | 5436 (25.9%) | 1657 (18.8%) | 0.170 | 25.6% | 25.6% | 0.000 |
| Stroke | 4524 (21.6%) | 1280 (14.5%) | 0.183 | 20.8% | 20.8% | 0.000 |
| Ischemic stroke | 3903 (18.6%) | 1068 (12.1%) | 0.180 | 18.4% | 18.4% | 0.000 |
| TIA | 2817 (13.4%) | 870 (9.9%) | 0.110 | 12.6% | 12.6% | 0.000 |
| CAD | 12574 (59.9%) | 5414 (61.5%) | 0.033 | 68.3% | 68.3% | 0.000 |
| PAD | 4434 (21.1%) | 1304 (14.8%) | 0.165 | 21.7% | 21.7% | 0.000 |
| Vascular disease (CAD or PAD) | 13138 (62.6%) | 5533 (62.9%) | 0.006 | 69.1% | 69.1% | 0.000 |
| Myocardial infarction | 5241 (25.0%) | 1984 (22.5%) | 0.057 | 33.2% | 33.2% | 0.000 |
| CABG | 3206 (15.3%) | 2067 (23.5%) | 0.209 | 31.3% | 31.3% | 0.000 |
| PCI | 3099 (14.8%) | 1223 (13.9%) | 0.025 | 22.0% | 22.0% | 0.000 |
| Left ventricular hypertrophy | 7508 (35.8%) | 3634 (41.3%) | 0.114 | 44.9% | 44.9% | 0.000 |
| Prior valve procedure | 2436 (11.6%) | 2577 (29.3%) | 0.449 | 21.8% | 21.8% | 0.000 |
| Mitral stenosis | 2114 (10.1%) | 991 (11.3%) | 0.039 | 15.1% | 15.1% | 0.000 |
| Mitral regurgitation | 9157 (43.6%) | 4842 (55.0%) | 0.230 | 55.1% | 55.1% | 0.000 |

**Table S6. Baseline Characteristics Before and After Propensity Score Weighting in Trial Ineligible Patients**

| | | | | | | |
|---|---|---|---|---|---|---|
| Major bleeding | 7497 (35.7%) | 2758 (31.3%) | 0.093 | 36.7% | 36.7% | 0.000 |
| Intracranial bleeding | 888 (4.2%) | 253 (2.9%) | 0.073 | 3.3% | 3.3% | 0.000 |
| Stage 3-5 CKD | 5486 (26.1%) | 1670 (19.0%) | 0.172 | 23.4% | 23.4% | 0.000 |
| Renal failure requiring dialysis | 1558 (7.4%) | 414 (4.7%) | 0.114 | 5.4% | 5.4% | 0.000 |
| Liver disease | 5358 (25.5%) | 1737 (19.7%) | 0.139 | 21.9% | 21.9% | 0.000 |
| Non skin cancer | 4438 (21.1%) | 1546 (17.6%) | 0.090 | 18.1% | 18.1% | 0.000 |
| Fall | 5370 (25.6%) | 1549 (17.6%) | 0.195 | 21.6% | 21.6% | 0.000 |
| Anemia | 13041 (62.1%) | 5209 (59.2%) | 0.060 | 61.5% | 61.5% | 0.000 |
| Alcoholism | 5234 (24.9%) | 1683 (19.1%) | 0.140 | 19.1% | 19.1% | 0.000 |
| Smoking | 9496 (45.2%) | 3881 (44.1%) | 0.023 | 46.7% | 46.7% | 0.000 |
| Hypothyroidism | 6479 (30.9%) | 2411 (27.4%) | 0.076 | 31.0% | 31.0% | 0.000 |
| Thyrotoxicosis | 1266 (6.0%) | 416 (4.7%) | 0.058 | 5.4% | 5.4% | 0.000 |
| Esophageal disease | 12080 (57.5%) | 4566 (51.9%) | 0.114 | 57.4% | 57.4% | 0.000 |
| Obesity | 7303 (34.8%) | 2991 (34.0%) | 0.017 | 37.2% | 37.2% | 0.000 |
| COPD | 5883 (28.0%) | 2069 (23.5%) | 0.103 | 26.9% | 26.9% | 0.000 |
| Obstructive sleep apnea | 5323 (25.4%) | 2611 (29.7%) | 0.097 | 28.6% | 28.6% | 0.000 |
| Hyperlipidemia | 17161 (81.8%) | 7117 (80.9%) | 0.022 | 83.4% | 83.4% | 0.000 |
| Osteoporosis | 3673 (17.5%) | 1173 (13.3%) | 0.116 | 14.9% | 14.9% | 0.000 |
| Pneumonia | 6876 (32.8%) | 2438 (27.7%) | 0.110 | 35.7% | 35.7% | 0.000 |
| Fracture | 5602 (26.7%) | 1906 (21.7%) | 0.118 | 28.0% | 28.0% | 0.000 |
| Dementia | 2737 (13.0%) | 558 (6.3%) | 0.228 | 10.8% | 10.8% | 0.000 |

**Table S6. Baseline Characteristics Before and After Propensity Score Weighting in Trial Ineligible Patients**

| | | | | | | |
|---|---|---|---|---|---|---|
| **Previous Drug Treatment** | | | | | | |
| N of previous AADs | | | | | | |
| 0 | 20811 (99.1%) | 217 (2.5%) | 7.572 | 36.3% | 36.3% | 0.000 |
| 1 | 178 (0.8%) | 7854 (89.3%) | 3.872 | 62.5% | 62.5% | 0.000 |
| 2+ | 3 (0.0%) | 728 (8.3%) | 0.424 | 1.2% | 1.2% | 0.000 |
| Amiodarone use | 124 (0.6%) | 5272 (59.9%) | 1.691 | 43.4% | 43.4% | 0.000 |
| N of previous rate control drugs | | | | | | |
| 0 | * | * | 0.488 | 0.4% | 0.4% | 0.000 |
| 1 | 12484 (59.5%) | 4335 (49.3%) | 0.206 | 52.1% | 52.1% | 0.000 |
| 2 | 5967 (28.4%) | 2452 (27.9%) | 0.012 | 29.8% | 29.8% | 0.000 |
| 3+ | * | * | 0.003 | 17.7% | 17.7% | 0.000 |
| **Concurrent Medication** | | | | | | |
| Oral anticoagulants | | | | | | |
| none | 16185 (77.1%) | 5658 (64.3%) | 0.284 | 76.1% | 76.1% | 0.000 |
| Warfarin | 2837 (13.5%) | 1459 (16.6%) | 0.086 | 13.0% | 13.0% | 0.000 |
| NOAC | 1970 (9.4%) | 1682 (19.1%) | 0.281 | 10.9% | 10.9% | 0.000 |
| ACE inhibitors | 4800 (22.9%) | 1957 (22.2%) | 0.015 | 24.3% | 24.3% | 0.000 |
| ARB | 2854 (13.6%) | 1070 (12.2%) | 0.043 | 11.4% | 11.4% | 0.000 |
| Thiazides | 2613 (12.4%) | 954 (10.8%) | 0.050 | 10.0% | 10.0% | 0.000 |
| Beta blockers (rate control) | 13724 (65.4%) | 4582 (52.1%) | 0.273 | 61.0% | 61.0% | 0.000 |
| Other beta blockers (not rate control) | 1099 (5.2%) | 323 (3.7%) | 0.076 | 4.3% | 4.3% | 0.000 |

**Table S6. Baseline Characteristics Before and After Propensity Score Weighting in Trial Ineligible Patients**

| | | | | | | |
|---|---|---|---|---|---|---|
| Calcium channel blockers (rate control) | 2598 (12.4%) | 801 (9.1%) | 0.106 | 8.9% | 8.9% | 0.000 |
| Other calcium channel blockers (not rate control) | 3467 (16.5%) | 1065 (12.1%) | 0.126 | 10.6% | 10.6% | 0.000 |
| Digitalis | 1112 (5.3%) | 354 (4.0%) | 0.060 | 5.1% | 5.1% | 0.000 |
| Diuretics--aldosterone antagonist | 1079 (5.1%) | 415 (4.7%) | 0.020 | 5.0% | 5.0% | 0.000 |
| Loop diuretics | 5041 (24.0%) | 2009 (22.8%) | 0.028 | 25.4% | 25.4% | 0.000 |
| Other antihypertensive drugs | 2067 (9.8%) | 600 (6.8%) | 0.110 | 7.7% | 7.7% | 0.000 |
| Statin | 8770 (41.8%) | 3773 (42.9%) | 0.022 | 41.9% | 41.9% | 0.000 |
| Insulin | 2025 (9.6%) | 490 (5.6%) | 0.154 | 8.7% | 8.7% | 0.000 |
| Metformin | 1572 (7.5%) | 578 (6.6%) | 0.036 | 8.5% | 8.5% | 0.000 |
| Other antidiabetic drugs | 1736 (8.3%) | 548 (6.2%) | 0.079 | 7.4% | 7.4% | 0.000 |
| Antiplatelet | 2241 (10.7%) | 614 (7.0%) | 0.131 | 10.7% | 10.7% | 0.000 |
| NSAIDs | 1926 (9.2%) | 701 (8.0%) | 0.043 | 8.6% | 8.6% | 0.000 |
| Antiulcer agents | 5871 (28.0%) | 2126 (24.2%) | 0.087 | 24.6% | 24.6% | 0.000 |
| Antidepressant | 5570 (26.5%) | 1715 (19.5%) | 0.168 | 25.9% | 25.9% | 0.000 |
| **$CHA_2DS_2$-VASc** | | | | | | |
| Mean (SD) | 4.1 (2.5) | 3.6 (2.4) | 0.194 | 4.1 (2.5) | 4.1 (2.5) | 0.000 |
| **$CHA_2DS_2$-VASc group** | | | | | | |
| 0-1 | 4689 (22.3%) | 2403 (27.3%) | 0.115 | 23.0% | 23.0% | 0.000 |
| 2-3 | 4040 (19.2%) | 1874 (21.3%) | 0.051 | 17.6% | 17.6% | 0.000 |
| 4+ | 12263 (58.4%) | 4522 (51.4%) | 0.142 | 59.5% | 59.5% | 0.000 |

**Table S6. Baseline Characteristics Before and After Propensity Score Weighting in Trial Ineligible Patients**

| | | | | | | |
|---|---|---|---|---|---|---|
| **Baseline period duration, years** | | | | | | |
| Mean (SD) | 5.3 (3.0) | 5.5 (3.2) | 0.066 | 5.6 (3.2) | 5.6 (3.2) | 0.000 |
| **Index year** | | | | | | |
| 2012 | 1419 (6.8%) | 610 (6.9%) | 0.007 | 7.9% | 7.9% | 0.000 |
| 2013 | 3727 (17.8%) | 1631 (18.5%) | 0.020 | 16.0% | 16.0% | 0.000 |
| 2014 | 3599 (17.1%) | 1425 (16.2%) | 0.025 | 18.9% | 18.9% | 0.000 |
| 2015 | 3480 (16.6%) | 1458 (16.6%) | 0.000 | 15.6% | 15.6% | 0.000 |
| 2016 | 4098 (19.5%) | 1761 (20.0%) | 0.012 | 19.4% | 19.4% | 0.000 |
| 2017 | 4669 (22.2%) | 1914 (21.8%) | 0.012 | 22.3% | 22.3% | 0.000 |
| **Health Utilization within past 12 months** | | | | | | |
| Number of emergency room visits | | | | | | |
| Mean (SD) | 1.0 (2.0) | 0.9 (1.5) | 0.079 | 1.0 (1.9) | 1.0 (2.0) | 0.000 |
| Number of inpatient stays | | | | | | |
| Mean (SD) | 1.1 (1.6) | 1.3 (1.4) | 0.121 | 1.1 (1.7) | 1.1 (1.3) | 0.000 |
| Number of days in hospital | | | | | | |
| Mean (SD) | 8.5 (15.9) | 10.1 (15.7) | 0.103 | 7.5 (15.1) | 7.5 (11.1) | 0.000 |
| Number of HF hospitalizations | | | | | | |
| Mean (SD) | 0.2 (0.6) | 0.2 (0.6) | 0.063 | 0.2 (0.8) | 0.2 (0.7) | 0.000 |

## Table S6. Baseline Characteristics Before and After Propensity Score Weighting in Trial Ineligible Patients

AAD denotes anti-arrhythmic drug, ACE angiotensin-converting enzyme, AF atrial fibrillation, ARB angiotensin II receptor blockers, CABG coronary artery bypass grafting, CAD coronary artery disease, CKD chronic kidney disease, COPD chronic obstructive pulmonary disease, CRT cardiac resynchronization therapy, HCM hypertrophic cardiomyopathy, ICD implantable cardioverter defibrillators, ILR implantable loop recorder, NSAID nonsteroidal anti-inflammatory drug, PAD peripheral artery disease, PCI percutaneous coronary intervention, PS propensity score, TIA transient ischemic attack.The $CHA_2DS_2$-VASc score is a 0- to 9-point stroke risk score where a higher point score indicates higher risk of stroke. The point score is calculated as follows: 1 point each for heart failure, hypertension, diabetes, vascular disease, age 65 to 74 years, and female sex and 2 points for age 75 years or older and prior thromboembolism (including ischemic stroke, TIA or systemic embolism). Concurrent medication use was defined as prescriptions within three months prior to the index date. * To maintain de-identification, OptumLabs does not allow researchers to disclose the number of events when the number is 10 or fewer.

**Table S7. Subgroup Analysis for the Secondary Outcome Stroke in Propensity Score Weighted Patients (Overall Cohort)**

| | Control | | | Early Rhythm-Control | | | Absolute Rate Difference (95% CI) | Hazard Ratio (95% CI) | P-value | P-value for interaction |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. of Events | Person Years | Event Rate | No. of Events | Person Years | Event Rate | | | | |
| **Age** | | | | | | | | | | **0,029** |
| <75 years | 17 | 1199 | 1,41 | 7 | 1236 | 0,58 | -0.83 (-1.44, -0.22) | 0.42 (0.26, 0.68) | <0.001 | |
| 75+ years | 20 | 986 | 2,04 | 17 | 955 | 1,77 | -0.28 (-1.17, 0.62) | 0.88 (0.55, 1.39) | 0,572 | |
| **Gender** | | | | | | | | | | **0,123** |
| Female | 16 | 876 | 1,79 | 14 | 888 | 1,52 | -0.27 (-1.15, 0.61) | 0.89 (0.53, 1.50) | 0,665 | |
| Male | 21 | 1.309 | 1,63 | 11 | 1.302 | 0,81 | -0.82 (-1.47, -0.18) | 0.49 (0.32, 0.77) | 0,002 | |
| **Race** | | | | | | | | | | **0,469** |
| Non-white | 12 | 450 | 2,61 | 7 | 476 | 1,39 | -1.22 (-2.64, 0.20) | 0.54 (0.29, 1.01) | 0,055 | |
| White | 25 | 1.735 | 1,46 | 17 | 1.715 | 1,01 | -0.44 (-0.99, 0.11) | 0.71 (0.47, 1.07) | 0,100 | |
| **$CHA_2DS_2$-VASc** | | | | | | | | | | **0,147** |
| 0-1 | 1 | 158 | 0,49 | 0 | 170 | 0,03 | -0.46 (-1.38, 0.47) | 0.07 (0.01, 0.77) | 0,030 | |
| 2-3 | 2 | 463 | 0,37 | 2 | 449 | 0,38 | 0.00 (-0.48, 0.49) | 1.00 (0.27, 3.68) | 0,995 | |
| 4+ | 35 | 1.564 | 2,24 | 22 | 1.571 | 1,40 | -0.79 (-1.50, -0.08) | 0.66 (0.46, 0.94) | 0,021 | |
| **Left Ventricular Hypertrophy** | | | | | | | | | | **0,653** |
| No prior LVH | 20 | 1336 | 1,47 | 13 | 1320 | 1,02 | -0.45 (-1.09, 0.19) | 0.70 (0.43, 1.13) | 0,148 | |
| Prior LVH | 17 | 850 | 2,05 | 11 | 871 | 1,22 | -0.83 (-1.72, 0.06) | 0.62 (0.38, 1.00) | 0,050 | |
| **Systolic HF** | | | | | | | | | | **0,640** |

**Table S7. Subgroup Analysis for the Secondary Outcome Stroke in Propensity Score Weighted Patients (Overall Cohort)**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| No prior SHF | 28 | 1708 | 1,64 | 17 | 1661 | 1,00 | -0.64 (-1.23, -0.06) | 0.62 (0.42, 0.92) | 0,017 | |
| Prior SHF | 9 | 477 | 1,89 | 7 | 529 | 1,41 | -0.48 (-1.65, 0.69) | 0.78 (0.40, 1.54) | 0,478 | |
| **Cardiomyopathy** | | | | | | | | | | **0,805** |
| No prior CM | 24 | 1528 | 1,58 | 15 | 1548 | 0,99 | -0.58 (-1.18, 0.02) | 0.65 (0.43, 0.99) | 0,043 | |
| Prior CM | 13 | 657 | 1,97 | 9 | 642 | 1,35 | -0.62 (-1.67, 0.43) | 0.67 (0.37, 1.22) | 0,192 | |
| **Obstructive Sleep Apnea** | | | | | | | | | | **0,187** |
| No prior OSA | 28 | 1608 | 1,75 | 20 | 1622 | 1,26 | -0.50 (-1.13, 0.13) | 0.73 (0.49, 1.08) | 0,117 | |
| Prior OSA | 9 | 577 | 1,54 | 4 | 568 | 0,65 | -0.89 (-1.81, 0.03) | 0.42 (0.22, 0.82) | 0,011 | |
| **Thromboembolism** | | | | | | | | | | **0,854** |
| No prior TE | 21 | 1662 | 1,27 | 14 | 1675 | 0,85 | -0.42 (-0.94, 0.10) | 0.68 (0.43, 1.07) | 0,092 | |
| Prior TE | 16 | 523 | 3,06 | 10 | 515 | 1,91 | -1.15 (-2.57, 0.28) | 0.65 (0.39, 1.08) | 0,097 | |

CI, confidence interval; LVH, left ventricular hypertrophy; SHF, systolic heart failure; CM, cardiomyopathy; OSA, obstructive sleep apnea; TE, thromboembolism.

**Table S8. Subgroup Analysis for the Secondary Outcome Hospitalization with the Diagnosis Heart Failure in Propensity Score Weighted Patients (Overall Cohort)**

| | Control | | | Early Rhythm-Control | | | Absolute Rate Difference (95% CI) | Hazard Ratio (95% CI) | P-value | P-value for interaction |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. of Events | Person Years | Event Rate | No. of Events | Person Years | Event Rate | | | | |
| **Age** | | | | | | | | | | **0,144** |
| <75 years | 36 | 1174 | 3,10 | 29 | 1207 | 2,40 | -0.70 (-1.69, 0.29) | 0.79 (0.56, 1.10) | 0,156 | |
| 75+ years | 47 | 951 | 4,97 | 49 | 916 | 5,38 | 0.41 (-1.06, 1.88) | 1.08 (0.81, 1.44) | 0,582 | |
| **Gender** | | | | | | | | | | **0,714** |
| Female | 32 | 855 | 3,73 | 32 | 863 | 3,68 | -0.05 (-1.35, 1.25) | 1.01 (0.72, 1.43) | 0,950 | |
| Male | 52 | 1.270 | 4,08 | 47 | 1.261 | 3,70 | -0.38 (-1.51, 0.75) | 0.90 (0.68, 1.20) | 0,482 | |
| **Race** | | | | | | | | | | **0,123** |
| Non-white | 26 | 426 | 6,03 | 19 | 458 | 4,25 | -1.78 (-4.08, 0.50) | 0.72 (0.48, 1.06) | 0,095 | |
| White | 58 | 1.700 | 3,41 | 59 | 1.665 | 3,54 | 0.12 (-0.78, 1.03) | 1.05 (0.81, 1.36) | 0,739 | |
| **$CHA_2DS_2$-VASc** | | | | | | | | | | **0,343** |
| 0-1 | 0 | 159 | 0,12 | 0 | 171 | 0,03 | -0.09 (-0.27, 0.09) | 0.28 (0.05, 1.52 | 0,139 | |
| 2-3 | 3 | 463 | 0,57 | 3 | 448 | 0,58 | 0.01 (-0.57, 0.60) | 1.01 (0.37, 2.78) | 0,978 | |
| 4+ | 81 | 1.503 | 5,38 | 76 | 1.505 | 5,03 | -0.35 (-1.55, 0.85) | 0.95 (0.76, 1.18) | 0,625 | |
| **Left Ventricular Hypertrophy** | | | | | | | | | | **0,796** |
| No prior LVH | 33 | 1318 | 2,52 | 32 | 1295 | 2,44 | -0.08 (-0.94, 0.78) | 0.97 (0.68, 1.36) | 0,843 | |
| Prior LVH | 51 | 808 | 6,25 | 47 | 828 | 5,65 | -0.60 (-2.35, 1.14) | 0.93 (0.70, 1.23) | 0,623 | |
| **Systolic HF** | | | | | | | | | | **0,686** |

**Table S8. Subgroup Analysis for the Secondary Outcome Hospitalization with the Diagnosis Heart Failure in Propensity Score Weighted Patients (Overall Cohort)**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| No prior SHF | 33 | 1698 | 1,95 | 27 | 1647 | 1,64 | -0.31 (-0.95, 0.33) | 0.85 (0.60, 1.19) | 0,338 | |
| Prior HF | 51 | 428 | 11,82 | 51 | 477 | 10,76 | -1.06 (-4.34, 2.22) | 0.95 (0.72, 1.26) | 0,729 | |
| **Cardiomyopathy** | | | | | | | | | | **0,001** |
| No prior CM | 47 | 1497 | 3,16 | 32 | 1526 | 2,08 | -1.08 (-1.95, -0.21) | 0.67 (0.49, 0.90) | 0,009 | |
| Prior CM | 36 | 628 | 5,79 | 47 | 597 | 7,79 | 2.01 (-0.04, 4.06) | 1.33 (0.97, 1.83) | 0,078 | |
| **Obstructive Sleep Apnea** | | | | | | | | | | **0,775** |
| No prior OSA | 56 | 1570 | 3,54 | 54 | 1579 | 3,39 | -0.15 (-1.08, 0.78) | 0.97 (0.75, 1.27) | 0,848 | |
| Prior OSA | 28 | 5,56 | 5,07 | 25 | 544 | 4,56 | -0.51 (-2.46, 1.44) | 0.89 (0.60, 1.32) | 0,556 | |
| **Thromboembolism** | | | | | | | | | | **0,914** |
| No prior TE | 55 | 1614 | 3,44 | 52 | 1627 | 3,21 | -0.23 (-1.15, 0.69) | 0.94 (0.72, 1.23) | 0,641 | |
| Prior TE | 28 | 511 | 5,51 | 26 | 497 | 5,27 | -0.24 (-2.30, 1.82) | 0.97 (0.67, 1.40) | 0,863 | |

CI, confidence interval; LVH, left ventricular hypertrophy; SHF, systolic heart failure; CM, cardiomyopathy; OSA, obstructive sleep apnea; TE, thromboembolism.

**Table S9. Subgroup Analysis for the Secondary Outcome Hospitalization with the Diagnosis Myocardial Infarction in Propensity Score Weighted Patients (Overall Cohort)**

| | Control | | | Early Rhythm-Control | | | Absolute Rate Difference (95% CI) | Hazard Ratio (95% CI) | P-value | P-value for interaction |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. of Events | Person Years | Event Rate | No. of Events | Person Years | Event Rate | | | | |
| **Age** | | | | | | | | | | **0,836** |
| <75 years | 13 | 1209 | 1,06 | 10 | 1230 | 0,85 | -0.21 (-0.75, 0.32) | 0.81 (0.48, 1.37) | 0,439 | |
| 75+ years | 21 | 994 | 2,08 | 15 | 957 | 1,55 | -0.54 (-1.43, 0.36) | 0.74 (0.47, 1.16) | 0,190 | |
| **Gender** | | | | | | | | | | **0,604** |
| Female | 12 | 885 | 1,34 | 10 | 891 | 1,14 | -0.20 (-0.95, 0.56) | 0.87 (0.49, 1.56) | 0,643 | |
| Male | 22 | 1.318 | 1,65 | 15 | 1.297 | 1,17 | -0.48 (-1.14, 0.17) | 0.70 (0.46, 1.08) | 0,107 | |
| **Race** | | | | | | | | | | **0,437** |
| Non-white | 6 | 465 | 1,35 | 6 | 475 | 1,34 | -0.01 (-1.03, 1.01) | 1.00 (0.47, 2.13) | 0,995 | |
| White | 27 | 1.738 | 1,57 | 19 | 1.712 | 1,11 | -0.47 (-1.03, 0.10) | 0.71 (0.48, 1.05) | 0,083 | |
| **$CHA_2DS_2$-VASc** | | | | | | | | | | **0,164** |
| 0-1 | 1 | 159 | 0,76 | 1 | 170 | 0,36 | -0.40 (-1.80, 0.99) | 0.48 (0.04, 5.46) | 0,550 | |
| 2-3 | 2 | 464 | 0,33 | 3 | 447 | 0,68 | 0.35 (-0.17, 0.87) | 2.06 (0.71, 5.98) | 0,184 | |
| 4+ | 31 | 1.580 | 1,95 | 22 | 1.571 | 1,38 | -0.58 (-1.24, 0.09) | 0.71 (0.50, 1.02) | 0,067 | |
| **Left Ventricular Hypertrophy** | | | | | | | | | | **0,332** |
| No prior LVH | 20 | 1348 | 1,48 | 13 | 1316 | 0,96 | -0.52 (-1.14, 0.10) | 0.65 (0.41, 1.03) | 0,064 | |
| Prior LVH | 14 | 855 | 1,59 | 13 | 871 | 1,45 | -0.14 (-0.96, 0.68) | 0.94 (0.56, 1.59) | 0,831 | |
| **Systolic HF** | | | | | | | | | | **0,577** |

**Table S9. Subgroup Analysis for the Secondary Outcome Hospitalization with the Diagnosis Myocardial Infarction in Propensity Score Weighted Patients (Overall Cohort)**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| No prior SHF | 25 | 1722 | 1,45 | 17 | 1658 | 1,03 | -0.42 (-0.98, 0.13) | 0.71 (0.47, 1.08) | 0,110 | |
| Prior HF | 9 | 481 | 1,78 | 8 | 530 | 1,55 | -0.23 (-1.34, 0.87) | 0.91 (0.49, 1.71) | 0,778 | |
| **Cardiomyopathy** | | | | | | | | | | **0,003** |
| No prior CM | 27 | 1536 | 1,74 | 14 | 1551 | 0,89 | -0.85 (-1.47, -0.24) | 0.52 (0.35, 0.78) | 0,001 | |
| Prior CM | 7 | 667 | 1,03 | 11 | 636 | 1,80 | 0.78 (-0.06, 1.62) | 1.75 (0.87, 3.50) | 0,114 | |
| **Obstructive Sleep Apnea** | | | | | | | | | | **0,385** |
| No prior OSA | 23 | 1622 | 1,45 | 19 | 1622 | 1,20 | -0.25 (-0.82, 0.32) | 0.84 (0.56, 1.27) | 0,410 | |
| Prior OSA | 10 | 581 | 1,75 | 6 | 565 | 1,03 | -0.71 (-1.70, 0.28) | 0.58 (0.31, 1.10) | 0,098 | |
| **Thromboembolism** | | | | | | | | | | **0,710** |
| No prior TE | 20 | 1677 | 1,21 | 16 | 1673 | 0,97 | -0.24 (-0.73, 0.25) | 0.80 (0.52, 1.23) | 0,313 | |
| Prior TE | 13 | 526 | 2,53 | 9 | 514 | 1,76 | -0.77 (-2.13, 0.58) | 0.72 (0.40, 1.28) | 0,266 | |

CI, confidence interval; LVH, left ventricular hypertrophy; SHF, systolic heart failure; CM, cardiomyopathy; OSA, obstructive sleep apnea; TE, thromboembolism.

**Table S10. Subgroup Analysis for the Secondary Outcome All-Cause Mortality in Propensity Score Weighted Patients (Overall Cohort)**

| | Control | | | Early Rhythm-Control | | | Absolute Rate Difference (95% CI) | Hazard Ratio (95% CI) | P-value | P-value for interaction |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. of Events | Person Years | Event Rate | No. of Events | Person Years | Event Rate | | | | |
| **Age** | | | | | | | | | | **0,151** |
| <75 years | 43 | 1228 | 3,50 | 32 | 1246 | 2,59 | -0.91 (-1.90, 0.08) | 0.74 (0.55, 1.00) | 0,049 | |
| 75+ years | 97 | 1015 | 9,55 | 90 | 977 | 9,18 | -0.37 (-2.22, 1.47) | 0.97 (0.79, 1.18) | 0,736 | |
| **Gender** | | | | | | | | | | **0,026** |
| Female | 70 | 899 | 7,78 | 50 | 906 | 5,56 | -2.23 (-3.97, -0.49) | 0.72 (0.56, 0.91) | 0,006 | |
| Male | 70 | 1.344 | 5,20 | 72 | 1.317 | 5,44 | 0.23 (-0.96, 1.42) | 1.04 (0.83, 1.31) | 0,709 | |
| **Race** | | | | | | | | | | **0,557** |
| Non-white | 28 | 473 | 5,89 | 28 | 483 | 5,71 | -0.18 (-2.32, 1.97) | 0.97 (0.68, 1.39) | 0,873 | |
| White | 112 | 1.770 | 6,33 | 94 | 1.739 | 5,42 | -0.91 (-2.03, 0.22) | 0.86 (0.71, 1.04) | 0,113 | |
| **$CHA_2DS_2$-VASc** | | | | | | | | | | **0,003** |
| 0-1 | 1 | 159 | 0,66 | 0 | 171 | 0,02 | -0.64 (-1.85, 0.56) | 0.03 (0.00, 0.22) | <0.001 | |
| 2-3 | 6 | 466 | 1,29 | 4 | 452 | 0,94 | -0.36 (-1.28, 0.57) | 0.74 (0.34, 1.58) | 0,436 | |
| 4+ | 133 | 1.617 | 8,23 | 118 | 1.601 | 7,37 | -0.86 (-2.22, 0.50) | 0.90 (0.76, 1.06) | 0,214 | |
| **Left Ventricular Hypertrophy** | | | | | | | | | | **0,196** |
| No prior LVH | 61 | 1374 | 4,44 | 58 | 1335 | 4,35 | -0.09 (-1.18, 1.00) | 0.99 (0.77, 1.27) | 0,908 | |
| Prior LVH | 79 | 869 | 9,07 | 64 | 888 | 7,19 | -1.88 (-3.78, 0.01) | 0.79 (0.64, 0.99) | 0,039 | |
| **Systolic HF** | | | | | | | | | | **0,731** |

**Table S10. Subgroup Analysis for the Secondary Outcome All-Cause Mortality in Propensity Score Weighted Patients (Overall Cohort)**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| No prior SHF | 79 | 1754 | 4,52 | 66 | 1683 | 3,92 | -0.60 (-1.55, 0.36) | 0.87 (0.70, 1.09) | 0,225 | |
| Prior HF | 61 | 489 | 12,40 | 56 | 540 | 10,36 | -2.04 (-4.94, 0.86) | 0.82 (0.64, 1.05) | 0,116 | |
| **Cardiomyopathy** | | | | | | | | | | **0,017** |
| No prior CM | 89 | 1567 | 5,69 | 66 | 1569 | 4,23 | -1.46 (-2.58, -0.35) | 0.75 (0.61, 0.92) | 0,006 | |
| Prior CM | 51 | 676 | 7,50 | 56 | 654 | 8,50 | 1.00 (-1.07, 3.08) | 1.13 (0.87, 1.48) | 0,356 | |
| **Obstructive Sleep Apnea** | | | | | | | | | | **0,565** |
| No prior OSA | 107 | 1647 | 6,52 | 92 | 1649 | 5,58 | -0.94 (-2.12, 0.24) | 0.86 (0.71, 1.03) | 0,106 | |
| Prior OSA | 33 | 5,96 | 5,46 | 30 | 574 | 5,21 | -0.25 (-2.11, 1.61) | 0.96 (0.68, 1.37) | 0,840 | |
| **Thromboembolism** | | | | | | | | | | **0,962** |
| No prior TE | 85 | 1696 | 5,01 | 75 | 1696 | 4,41 | -0.59 (-1.62, 0.43) | 0.88 (0.71, 1.09) | 0,251 | |
| Prior TE | 55 | 547 | 10,05 | 47 | 527 | 8,94 | -1.11 (-3.71, 1.50) | 0.89 (0.68, 1.16) | 0,379 | |

CI, confidence interval; LVH, left ventricular hypertrophy; SHF, systolic heart failure; CM, cardiomyopathy; OSA, obstructive sleep apnea; TE, thromboembolism.

**Table S11. Subgroup Analysis for the Primary Outcome in Propensity Score Weighted Patients (Trial Eligible Patients)**

| | Control | | | Early Rhythm-Control | | | Absolute Rate Difference (95% CI) | Hazard Ratio (95% CI) | P-value | P-value for interaction |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. of Events | Person Years | Event Rate | No. of Events | Person Years | Event Rate | | | | |
| **Age** | | | | | | | | | | **0,136** |
| <75 years | 52 | 741 | 7,02 | 41 | 759 | 5,35 | -1.67 (-3.52, 0.18) | 0.76 (0.57, 1.00) | 0,053 | |
| 75+ years | 113 | 765 | 14,81 | 102 | 707 | 14,50 | -0.31 (-3.01, 2.38) | 0.98 (0.82, 1.18) | 0,845 | |
| **Gender** | | | | | | | | | | **0,595** |
| Female | 73 | 633 | 11,50 | 61 | 630 | 9,75 | -1.74 (-4.36, 0.88) | 0.85 (0.67, 1.07) | 0,162 | |
| Male | 93 | 874 | 10,60 | 82 | 836 | 9,77 | -0.83 (-2.95, 1.28) | 0.92 (0.75, 1.13) | 0,441 | |
| **Race** | | | | | | | | | | **0,282** |
| Non-white | 38 | 284 | 13,29 | 32 | 316 | 10,07 | -3.22 (-7.29, 0.85) | 0.77 (0.56, 1.06) | 0,108 | |
| White | 128 | 1.222 | 10,44 | 111 | 12 | 9,68 | -0.76 (-2.56 (1.04) | 0.93 (0.78, 1.11) | 0,408 | |
| **$CHA_2DS_2$-VASc** | | | | | | | | | | **0,930** |
| 0-1 | 1 | 12 | 6,82 | 1 | 15 | 3,90 | -2.92 (-16.55, 10.70) | 0.51 (0.07, 3.47) | 0,493 | |
| 2-3 | 9 | 356 | 2,65 | 8 | 333 | 2,42 | -0.23 (-1.78, 1.31) | 0.92 (0.51, 1.67) | 0,794 | |
| 4+ | 155 | 1.139 | 13,60 | 134 | 1.118 | 11,99 | -1.59 (-3.71, 0.52) | 0.88 (0.75, 1.04) | 0,128 | |
| **Left Ventricular Hypertrophy** | | | | | | | | | | **0,879** |
| No prior LVH | 85 | 931 | 9,12 | 75 | 913 | 8,23 | -0.89 (-2.82, 1.04) | 0.90 (0.73, 1.12) | 0,362 | |
| Prior LVH | 80 | 575 | 13,99 | 68 | 5,53 | 12,3 | -1.69 (-4.65, 1.26) | 0.89 (0.71, 1.10) | 0,283 | |
| **Systolic HF** | | | | | | | | | | **0,858** |

**Table S11. Subgroup Analysis for the Primary Outcome in Propensity Score Weighted Patients (Trial Eligible Patients)**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| No prior SHF | 103 | 1223 | 8,41 | 84 | 1162 | 7,21 | -1.20 (-2.78, 0.38) | 0.86 (0.71, 1.05) | 0,131 | |
| Prior HF | 62 | 283 | 22,08 | 59 | 304 | 19,52 | -2.46 (-7.68, 2.56) | 0.88 (0.70, 1.11) | 0,286 | |
| **Cardiomyopathy** | | | | | | | | | | **<0.001** |
| No prior CM | 109 | 1059 | 10,30 | 78 | 1048 | 7,42 | -2.88 (-4.72, -1.04) | 0.72 (0.59, 0.87) | 0,001 | |
| Prior CM | 56 | 448 | 12,58 | 65 | 418 | 15,65 | 3.07 (-0.41, 6.54) | 1.24 (0.96, 1.61) | 0,094 | |
| **Obstructive Sleep Apnea** | | | | | | | | | | **0,728** |
| No prior OSA | 124 | 1106 | 11,19 | 107 | 1095 | 9,79 | -1.40 (-3.32, 0.51) | 0.88 (0.73, 1.04) | 0,139 | |
| Prior OSA | 42 | 400 | 10,39 | 36 | 371 | 9,69 | -0.70 (-3.93, 2.52) | 0.93 (0.68, 1.28) | 0,663 | |
| **Thromboembolism** | | | | | | | | | | **0,053** |
| No prior TE | 102 | 1168 | 8,72 | 97 | 1120 | 8,61 | -0.11 (-1.79, 1.58) | 0.99 (0.81, 1.20) | 0,902 | |
| Prior TE | 64 | 339 | 18,76 | 47 | 345 | 13,48 | -5.28 (-9.65, -0.91) | 0.72 (0.56, 0.93) | 0,012 | |

CI, confidence interval; LVH, left ventricular hypertrophy; SHF, systolic heart failure; CM, cardiomyopathy; OSA, obstructive sleep apnea; TE, thromboembolism.

**Table S12. Subgroup Analysis for the Primary Outcome in Propensity Score Weighted Patients (Trial Ineligible Patients)**

| | Control | | | Early Rhythm-Control | | | Absolute Rate Difference (95% CI) | Hazard Ratio (95% CI) | P-value | P-value for interaction |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. of Events | Person Years | Event Rate | No. of Events | Person Years | Event Rate | | | | |
| **Age** | | | | | | | | | | **0,123** |
| <75 years | 32 | 394 | 8,09 | 21 | 427 | 4,98 | -3.10 (-5.76, -0.45) | 0.62 (0.44, 0.88) | 0,006 | |
| 75+ years | 31 | 149 | 20,71 | 31 | 172 | 17,89 | -2.81 (-10.22, 4.59) | 0.91 (0.64, 1.30) | 0,611 | |
| **Gender** | | | | | | | | | | **0,814** |
| Female | 26 | 191 | 13,54 | 22 | 203 | 10,59 | -2.95 (-8.13, 2.24) | 0.78 (0.53, 1.14) | 0,197 | |
| Male | 37 | 351 | 10,46 | 31 | 396 | 7,72 | -2.74 (-6.04, 0.56) | 0.75 (0.54, 1.04) | 0,083 | |
| **Race** | | | | | | | | | | **0,624** |
| Non-white | 18 | 123 | 14,41 | 16 | 127 | 12,24 | -2.17 (-9.44, 5.10) | 0.82 (0.52, 1.31) | 0,410 | |
| White | 45 | 420 | 10,71 | 37 | 472 | 7,74 | -2.97 (-5.95, 0.00) | 0.73 (0.55, 0.98) | 0,036 | |
| **$CHA_2DS_2$-VASc** | | | | | | | | | | **0,023** |
| 0-1 | 1 | 145 | 0,99 | 0 | 155 | 0,10 | -0.88 (-2.25, 0.48) | 0.11 (0.02, 0.50) | 0,004 | |
| 2-3 | 1 | 102 | 1,27 | 2 | 108 | 1,74 | 0.47 (-0.94, 1.88) | 1.37 (0.49, 3.87) | 0,550 | |
| 4+ | 60 | 296 | 20,27 | 50 | 336 | 14,86 | -5.38 (-10.68, -0.00) | 0.75 (0.58, 0.97) | 0,028 | |
| **Left Ventricular Hypertrophy** | | | | | | | | | | **0,092** |
| No prior LVH | 18 | 337 | 5,30 | 19 | 350 | 5,31 | 0.00 (-2.40, 2.42) | 1.01 (0.64, 1.59) | 0,962 | |
| Prior LVH | 45 | 206 | 21,76 | 34 | 249 | 13,44 | -8.32 (-14.73, -1.91) | 0.63 (0.47, 0.86) | 0,003 | |

**Table S12. Subgroup Analysis for the Primary Outcome in Propensity Score Weighted Patients (Trial Ineligible Patients)**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Systolic HF** | | | | | | | | | | **0,959** |
| No prior SHF | 28 | 414 | 6,88 | 22 | 440 | 4,98 | -1.90 (-4.27, 0.48) | 0.75 (0.52, 1.08) | 0,121 | |
| Prior HF | 34 | 129 | 26,54 | 30 | 159 | 18,94 | -7.60 (-16.96, 1.77) | 0.74 (0.53, 1.04) | 0,085 | |
| **Cardiomyopathy** | | | | | | | | | | **0,126** |
| No prior CM | 36 | 386 | 9,30 | 26 | 445 | 5,87 | -3.43 (-6.28, -0.58) | 0.65 (0.47, 0.91) | 0,011 | |
| Prior CM | 27 | 157 | 17,08 | 26 | 154 | 16,83 | -0.24 (-7.36, 6.87) | 0.98 (0.67, 1.42) | 0,903 | |
| **Obstructive Sleep Apnea** | | | | | | | | | | **0,330** |
| No prior OSA | 44 | 416 | 10,53 | 38 | 439 | 8,59 | -1.94 (-5.02, 1.15) | 0.82 (0.61, 1.11) | 0,199 | |
| Prior OSA | 19 | 126 | 14,89 | 14 | 160 | 8,97 | -5.92 (-12.17, 0.33) | 0.63 (0.40, 0.99) | 0,043 | |
| **Thromboembolism** | | | | | | | | | | **0,130** |
| No prior TE | 37 | 404 | 9,27 | 28 | 469 | 5,99 | -3.28 (-6.12, -0.43) | 0.67 (0.49, 0.93) | 0,016 | |
| Prior TE | 25 | 138 | 18,21 | 24 | 131 | 18,39 | 0.18 (-7.34, 7.70) | 1.01 (0.68, 1.48) | 0,978 | |

CI, confidence interval; LVH, left ventricular hypertrophy; SHF, systolic heart failure; CM, cardiomyopathy; OSA, obstructive sleep apnea; TE, thromboembolism.

**Table S13. Sensitivity Analyses Stratified by Treatment with AF Ablation or without AF Ablation in the Early Rhythm-Control Therapy Cohort**

| | Control | | | Early Rhythm-Control | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. of Events | Person Years | Event Rate | No. of Events | Person Years | Event Rate | Absolute Rate Difference (95% CI) | Hazard Ratio (95% CI) | P Value |
| **Overall cohort - with AF ablation** | **N=82,633** | | | **N=2470** | | | | | |
| Composite | 33 | 605 | 5.40 | 26 | 586 | 4.36 | -1.05 (-2.84, 0.75) | 0.80 (0.55, 1.18) | 0.261 |
| Stroke | 5 | 625 | 0.76 | 4 | 608 | 0.64 | -0.12 (-0.80, 0.57) | 0.87 (0.32, 2.39) | 0.786 |
| HF | 12 | 619 | 1.94 | 14 | 593 | 2.44 | 0.50 (-0.79, 1.78) | 1.27 (0.72, 2.23) | 0.409 |
| MI | 5 | 627 | 0.81 | 3 | 610 | 0.46 | -0.35 (-0.89, 0.18) | 0.57 (0.24, 1.37) | 0.209 |
| Mortality | 19 | 633 | 3.05 | 14 | 614 | 2.26 | -0.79 (-2.09, 0.50) | 0.74 (0.44, 1.24) | 0.250 |
| **Overall cohort - without AF ablation (AAD only)** | **N=82,633** | | | **N=24,636** | | | | | |
| Composite | 177 | 1,333 | 13.28 | 154 | 1,353 | 11.39 | -1.89 (-3.87, 0.10) | 0.86 (0.74, 1.00) | 0.048 |
| Stroke | 29 | 1,440 | 2.00 | 18 | 1,447 | 1.23 | -0.77 (-1.46, -0.07) | 0.62 (0.43, 0.90) | 0.013 |
| HF | 65 | 1,387 | 4.67 | 58 | 1,402 | 4.14 | -0.53 (-1.70, 0.63) | 0.89 (0.70, 1.15) | 0.388 |
| MI | 25 | 1,454 | 1.74 | 21 | 1,442 | 1.48 | -0.27 (-0.94, 0.41) | 0.86 (0.58, 1.27) | 0.440 |
| Mortality | 110 | 1,484 | 7.42 | 99 | 1,471 | 6.71 | -0.71 (-2.09, 0.68) | 0.91 (0.75, 1.10) | 0.323 |
| **Eligible for Trial -with AF ablation** | **N=61,641** | | | **N=1543** | | | | | |
| Composite | 26 | 425 | 6.16 | 21 | 387 | 5.51 | -0.65 (-3.09, 1.78) | 0.89 (0.58, 1.35) | 0.583 |

**Table S13. Sensitivity Analyses Stratified by Treatment with AF Ablation or without AF Ablation in the Early Rhythm-Control Therapy Cohort**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Stroke | 4 | 439 | 0.95 | 4 | 406 | 0.96 | 0.01 (-0.98, 1.01) | 1.05 (0.37, 3.02) | 0.924 |
| HF | 8 | 437 | 1.91 | 11 | 394 | 2.85 | 0.95 (-0.72, 2.62) | 1.48 (0.77, 2.85) | 0.234 |
| MI | 4 | 442 | 0.99 | 3 | 408 | 0.63 | -0.36 (-1.11, 0.39) | 0.63 (0.24, 1.65) | 0.349 |
| Mortality | 16 | 447 | 3.57 | 11 | 413 | 2.61 | -0.96 (-2.66, 0.75) | 0.74 (0.41, 1.32) | 0.306 |
| **Eligible for Trial -without AF ablation (AAD only)** | | **N=61,641** | | | **N=16,764** | | | | |
| Composite | 129 | 1,023 | 12.57 | 110 | 1,006 | 10.95 | -1.62 (-3.78, 0.54) | 0.87 (0.73, 1.04) | 0.122 |
| Stroke | 24 | 1,093 | 2.24 | 14 | 1,071 | 1.31 | -0.93 (-1.78, -0.08) | 0.60 (0.40, 0.90) | 0.013 |
| HF | 43 | 1,064 | 4.09 | 40 | 1,041 | 3.81 | -0.28 (-1.52, 0.96) | 0.94 (0.69, 1.27) | 0.685 |
| MI | 20 | 1,104 | 1.77 | 15 | 1,069 | 1.40 | -0.36 (-1.14, 0.41) | 0.80 (0.51, 1.26) | 0.345 |
| Mortality | 82 | 1,127 | 7.27 | 68 | 1,090 | 6.26 | -1.01 (-2.56, 0.54) | 0.86 (0.69, 1.08) | 0.193 |
| **Ineligible for Trial -with AF ablation** | | **N=20,992** | | | **N=927** | | | | |
| Composite | 6 | 180 | 3.61 | 4 | 199 | 2.11 | -1.50 (-3.78, 0.77) | 0.54 (0.24, 1.23) | 0.144 |
| Stroke | 1 | 186 | 0.31 | 0 | 201 | 0.00 | -0.31 (-0.72, 0.09) | 0.00 (0.00, 0.00) | <0.001 |
| HF | 4 | 181 | 2.02 | 3 | 199 | 1.60 | -0.42 (-2.38, 1.55) | 0.76 (0.26, 2.20) | 0.610 |
| MI | 1 | 185 | 0.38 | 0 | 201 | 0.11 | -0.27 (-0.73, 0.18) | 0.31 (0.06, 1.59) | 0.160 |
| Mortality | 3 | 186 | 1.81 | 3 | 201 | 1.54 | -0.27 (-2.04, 1.50) | 0.79 (0.28, 2.21) | 0.654 |
| **Ineligible for Trial -without AF ablation (AAD only)** | | **N=20,992** | | | **N=7872** | | | | |
| Composite | 49 | 311 | 15.62 | 44 | 347 | 12.68 | -2.94 (-7.67, 1.78) | 0.82 (0.61, 1.10) | 0.186 |
| Stroke | 4 | 347 | 1.23 | 4 | 376 | 1.00 | -0.23 (-1.30, 0.84) | 0.82 (0.34, 1.96) | 0.650 |

**Table S13. Sensitivity Analyses Stratified by Treatment with AF Ablation or without AF Ablation in the Early Rhythm-Control Therapy Cohort**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| HF | 21 | 323 | 6.59 | 18 | 360 | 5.09 | -1.50 (-4.43, 1.42) | 0.80 (0.51, 1.25) | 0.320 |
| MI | 6 | 350 | 1.67 | 6 | 373 | 1.68 | 0.01 (-1.38, 1.40) | 1.02 (0.44, 2.33) | 0.970 |
| Mortality | 28 | 357 | 7.90 | 31 | 381 | 8.02 | 0.12 (-2.86, 3.10) | 1.03 (0.71, 1.50) | 0.880 |

First, we recalculated the propensity score weights to balance patients treated with early rhythm-control and patients treated without early rhythm-control and performed regression analyses to compare early rhythm-control to the control group; we then recalculated the weights to balance patients treated with AF ablation and patients treated without early rhythm-control and performed regression analyses to compare AF ablation to the control group. Patients treated with both AAD therapy and AF ablation were classified to the ablation group. AAD, anti-arrhythmic drug; AF, atrial fibrillation; CI, confidence interval; HF, hospitalization with the diagnosis heart failure; MI, hospitalization with the diagnosis myocardial infarction.

**Table S14. Sensitivity Analyses Stratified by Adherence to AADs in the Early Rhythm-Control Cohort (Overall Cohort)**

| | Control | | | Early Rhythm-Control | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. of Events | Person Years | Event Rate | No. of Events | Person Years | Event Rate | Absolute Rate Difference (95% CI) | Hazard Ratio (95% CI) | P Value |
| **Non-adherent** | | **N=82,633** | | | **N=18,822** | | | | |
| Composite | 170 | 1,284 | 13.21 | 145 | 1,303 | 11.14 | -2.06 (-4.08, -0.05) | 0.85 (0.73, 0.99) | 0.033 |
| Stroke | 28 | 1,386 | 1.99 | 20 | 1,393 | 1.41 | -0.58 (-1.30, 0.13) | 0.72 (0.49, 1.06) | 0.093 |
| HF | 62 | 1,335 | 4.67 | 54 | 1,353 | 4.02 | -0.65 (-1.84, 0.54) | 0.87 (0.68, 1.13) | 0.311 |
| MI | 24 | 1,400 | 1.73 | 19 | 1,393 | 1.40 | -0.33 (-1.02, 0.35) | 0.82 (0.54, 1.24) | 0.344 |
| Mortality | 105 | 1,428 | 7.38 | 91 | 1,420 | 6.40 | -0.98 (-2.38, 0.42) | 0.87 (0.72, 1.06) | 0.166 |
| **Adherent** | | **N=82,633** | | | **N=5814** | | | | |
| Composite | 124 | 885 | 14.00 | 115 | 906 | 12.69 | -1.31 (-3.82, 1.20) | 0.91 (0.76, 1.08) | 0.281 |
| Stroke | 18 | 963 | 1.90 | 9 | 977 | 0.95 | -0.95 (-1.72, -0.18) | 0.50 (0.31, 0.82) | 0.006 |
| HF | 47 | 917 | 5.13 | 43 | 931 | 4.62 | -0.51 (-2.02, 1.00) | 0.90 (0.66, 1.21) | 0.474 |
| MI | 17 | 971 | 1.70 | 15 | 969 | 1.53 | -0.17 (-0.99, 0.64) | 0.90 (0.55, 1.48) | 0.675 |
| Mortality | 77 | 989 | 7.80 | 77 | 988 | 7.81 | 0.01 (-1.76, 1.79) | 1.00 (0.80, 1.26) | 0.994 |

Adherence was defined as proportion of days covered (PDC) ≥80% in the timeframe between first AF date to index date. The adherence considered all rhythm-control drugs that patients used, even if they were different from the initial treatment. We first recalculated the propensity score weights to balance patients who were treated with AADs who were adherent and patients who were treated without early rhythm-control, and performed regression analyses to compare patients treated without early rhythm-control to adherent AAD-treated patients; we then recalculated the weights to balance patients who were treated without early rhythm-control and patients who were treated with AADs who were not adherent, and performed regression analyses to compare patients treated without early rhythm-control to non-adherent AAD-treated patients. AAD, anti-arrhythmic drug; CI, confidence interval; HF, hospitalization with the diagnosis heart failure; MI, hospitalization with the diagnosis myocardial infarction.

**Table S15. Sensitivity Analyses Stratified by Adherence to AADs in the Early Rhythm-Control Cohort (Trial Eligible)**

| | Control | | | Early Rhythm-Control | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. of Events | Person Years | Event Rate | No. of Events | Person Years | Event Rate | Absolute Rate Difference (95% CI) | Hazard Ratio (95% CI) | P Value |
| **Non-adherent** | | **N=61,641** | | | **N=12,365** | | | | |
| Composite | 123 | 983 | 12.48 | 102 | 966 | 10.59 | -1.89 (-4.08, 0.30) | 0.85 (0.71, 1.02) | 0.074 |
| Stroke | 24 | 1,050 | 2.24 | 16 | 1,027 | 1.54 | -0.70 (-1.58, 0.17) | 0.71 (0.46, 1.07) | 0.104 |
| HF | 42 | 1,022 | 4.07 | 36 | 1,002 | 3.60 | -0.48 (-1.73, 0.78) | 0.89 (0.65, 1.22) | 0.484 |
| MI | 19 | 1,061 | 1.75 | 14 | 1,029 | 1.33 | -0.42 (-1.20, 0.36) | 0.78 (0.48, 1.24) | 0.288 |
| Mortality | 78 | 1,082 | 7.22 | 62 | 1,048 | 5.93 | -1.30 (-2.87, 0.28) | 0.82 (0.65, 1.03) | 0.092 |
| **Adherent** | | **N=61,641** | | | **N=4399** | | | | |
| Composite | 94 | 691 | 13.54 | 89 | 677 | 13.18 | -0.36 (-3.16, 2.45) | 0.97 (0.79, 1.20) | 0.794 |
| Stroke | 16 | 745 | 2.15 | 7 | 732 | 0.92 | -1.23 (-2.14, -0.31) | 0.43 (0.25, 0.74) | 0.002 |
| HF | 33 | 717 | 4.56 | 33 | 698 | 4.71 | 0.15 (-1.49, 1.80) | 1.02 (0.71, 1.45) | 0.919 |
| MI | 14 | 751 | 1.83 | 11 | 724 | 1.59 | -0.24 (-1.23, 0.74) | 0.86 (0.49, 1.50) | 0.589 |
| Mortality | 60 | 766 | 7.79 | 59 | 740 | 7.98 | 0.19 (-1.85, 2.23) | 1.02 (0.79, 1.33) | 0.853 |

Adherence was defined as proportion of days covered (PDC) ≥80% in the timeframe between first AF date to index date. The adherence considered all rhythm-control drugs that patients used, even if they were different from the initial treatment. We first recalculated the propensity score weights to balance patients who were treated with AADs who were adherent and patients who were treated without early rhythm-control, and performed regression analyses to compare patients treated without early rhythm-control to adherent AAD-treated patients; we then recalculated the weights to balance patients who were treated without early rhythm-control and patients who were treated with AADs who were not adherent, and performed regression analyses to compare patients treated without early rhythm-control to non-adherent AAD-treated patients. AAD, anti-arrhythmic drug; CI, confidence interval; HF, hospitalization with the diagnosis heart failure; MI, hospitalization with the diagnosis myocardial infarction.

**Table S16. Sensitivity Analyses Stratified by Adherence to AADs in the Early Rhythm-Control Cohort (Trial Ineligible)**

| | Control | | | Early Rhythm-Control | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. of Events | Person Years | Event Rate | No. of Events | Person Years | Event Rate | Absolute Rate Difference (95% CI) | Hazard Ratio (95% CI) | P Value |
| **Non-adherent** | | **N=20,992** | | | **N=6,457** | | | | |
| Composite | 47 | 301 | 15.58 | 43 | 336 | 12.73 | -2.86 (-7.65, 1.94) | 0.83 (0.62, 1.11) | 0.212 |
| Stroke | 4 | 336 | 1.21 | 4 | 366 | 1.04 | -0.17 (-1.26, 0.92) | 0.87 (0.35, 2.15) | 0.759 |
| HF | 21 | 313 | 6.60 | 18 | 351 | 5.23 | -1.37 (-4.36, 1.62) | 0.82 (0.52, 1.29) | 0.396 |
| MI | 6 | 339 | 1.67 | 6 | 364 | 1.59 | -0.08 (-1.49, 1.33) | 0.96 (0.41, 2.25) | 0.922 |
| Mortality | 27 | 346 | 7.85 | 29 | 372 | 7.74 | -0.12 (-3.13, 2.90) | 1.00 (0.68, 1.46) | 0.995 |
| **Adherent** | | **N=20,992** | | | **N=1415** | | | | |
| Composite | 30 | 194 | 15.62 | 26 | 229 | 11.22 | -4.39 (-10.11, 1.32) | 0.73 (0.50, 1.05) | 0.093 |
| Stroke | 2 | 218 | 1.06 | 3 | 245 | 1.04 | -0.01 (-1.28, 1.25) | 1.03 (0.31, 3.34) | 0.967 |
| HF | 14 | 200 | 7.19 | 10 | 233 | 4.35 | -2.83 (-6.47, 0.81) | 0.63 (0.36, 1.10) | 0.105 |
| MI | 3 | 220 | 1.27 | 3 | 245 | 1.34 | 0.08 (-1.23, 1.39) | 1.11 (0.40, 3.06) | 0.842 |
| Mortality | 18 | 223 | 7.85 | 18 | 248 | 7.31 | -0.54 (-4.16, 3.08) | 0.94 (0.59, 1.50) | 0.793 |

Adherence was defined as proportion of days covered (PDC) ≥80% in the timeframe between first AF date to index date. The adherence considered all rhythm-control drugs that patients used, even if they were different from the initial treatment. We first recalculated the propensity score weights to balance patients who were treated with AADs who were adherent and patients who were treated without early rhythm-control, and performed regression analyses to compare patients treated without early rhythm-control to adherent AAD-treated patients; we then recalculated the weights to balance patients who were treated without early rhythm-control and patients who were treated with AADs who were not adherent, and performed regression analyses to compare patients treated without early rhythm-control to non-adherent AAD-treated patients. AAD, anti-arrhythmic drug; CI, confidence interval; HF, hospitalization with the diagnosis heart failure; MI, hospitalization with the diagnosis myocardial infarction.

## Table S17. Falsification Endpoint Test in Propensity Score Weighted Cohort

| | Hazard Ratio | p |
|---|---|---|
| **Pneumonia** | | |
| Overall | 1.00 (0.79, 1.28) | 0.972 |
| Eligible | 0.96 (0.72, 1.28) | 0.801 |
| Ineligible | 1.33 (0.83, 2.14) | 0.236 |
| **Fracture** | | |
| Overall | 1.14 (0.90, 1.44) | 0.289 |
| Eligible | 1.15 (0.87, 1.51) | 0.333 |
| Ineligible | 1.27 (0.78. 2.07) | 0.327 |

Outcomes were captured by primary diagnosis during an emergency room visit or an inpatient stay.