ORIGINAL RESEARCH

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

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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 sets3; 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 (CHA2-DKS-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...
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). 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. 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.

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.

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. 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). 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 m² 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.

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 |
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 eligibility. The standardized mean difference was used to assess the balance of covariates after weighting and a difference <0.1 was considered acceptable.\textsuperscript{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). The proportional hazards assumption was tested on the basis of Schoenfeld residuals. 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, CHA2DS2-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, 71.0±11.6 years, 52,417 patients (47.8%) were women, 21,582 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 CHA2DS2-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 CHA2DS2-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)
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 the 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 CHA2DS2-VASc score was 4.6 in OptumLabs compared with 3.4 in EAST-AFNET 4). Interestingly, the
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 CHA2DS2-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

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

| 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.
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%.\textsuperscript{24–28} The information contained in health data sets such as OptumLabs is less precise.
than the more granular information collected in a clinical trial, hence excluding cause of death in this analysis, which could 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                             |                          |                               |                       |                   |
| <75 years                       | 42869/84/1135/7.39       | 17483/62/1186/5.22            | 0.71 (0.57, 0.88)     | 0.026             |
| 75+ years                       | 39764/144/914/15.77      | 9623/133/879/15.16            | 0.96 (0.82, 1.14)     |                   |
|                                 |                          |                               |                       |                   |
|                                 |                          |                                |                       |                   |
| Sex                             |                          |                                |                       |                   |
| Female                          | 41368/99/824/11.97       | 11049/83/834/9.96             | 0.83 (0.68, 1.01)     | 0.789             |
| Male                            | 41265/129/1225/10.56     | 16057/112/1232/9.11           | 0.86 (0.75, 1.03)     |                   |
|                                 |                          |                                |                       |                   |
|                                 |                          |                                |                       |                   |
|                                 |                          |                                |                       |                   |
| Race                            |                          |                                |                       |                   |
| Asian/Black/Hispanic/Unknown    | 19140/55/407/13.65       | 5116/47/443/10.69             | 0.79 (0.61, 1.03)     | 0.543             |
| White                           | 63493/173/1642/10.51     | 21990/148/1622/9.11           | 0.87 (0.75, 1.01)     |                   |
|                                 |                          |                                |                       |                   |
|                                 |                          |                                |                       |                   |
| CHA2DS2-VASc                    |                          |                                |                       |                   |
| 0-1                             | 5173/2/157/1.43          | 2724/1/170/0.44               | 0.31 (0.05, 2.00)     | 0.508             |
| 2-3                             | 17768/31/458/2.34        | 7153/10/442/2.25              | 0.97 (0.57, 1.64)     |                   |
| 4+                              | 59602/215/1435/14.98     | 17229/185/1454/12.72          | 0.85 (0.74, 0.97)     |                   |
|                                 |                          |                                |                       |                   |
| Left ventricular hypertrophy    |                          |                                |                       |                   |
| No                              | 54884/103/1268/8.10      | 10603/94/1263/7.42            | 0.92 (0.75, 1.11)     | 0.277             |
| Yes                             | 27749/125/781/16.04      | 11043/101/802/12.65           | 0.80 (0.67, 0.95)     |                   |
|                                 |                          |                                |                       |                   |
|                                 |                          |                                |                       |                   |
| Systolic heart failure          |                          |                                |                       |                   |
| No                              | 68661/131/1637/8.02      | 20996/106/1602/6.60           | 0.83 (0.69, 0.98)     | 0.987             |
| Yes                             | 13972/97/412/23.47       | 6119/89/463/19.32            | 0.83 (0.68, 1.01)     |                   |
|                                 |                          |                                |                       |                   |
|                                 |                          |                                |                       |                   |
| Cardiomyopathy                  |                          |                                |                       |                   |
| No                              | 66463/145/1445/10.03     | 20301/104/1493/6.95           | 0.69 (0.59, 0.82)     | 0.001             |
| Yes                             | 16170/83/605/13.75       | 6805/91/572/15.97            | 1.16 (0.94, 1.43)     |                   |
|                                 |                          |                                |                       |                   |
| Obstructive sleep apnea         |                          |                                |                       |                   |
| No                              | 64736/168/1523/11.01     | 19314/145/1534/9.44           | 0.86 (0.74, 1.00)     | 0.803             |
| Yes                             | 17987/60/527/11.47       | 7992/50/531/10.47            | 0.82 (0.63, 1.06)     |                   |
|                                 |                          |                                |                       |                   |
| Thromboembolism                 |                          |                                |                       | 0.457             |
| No                              | 61012/139/1572/8.86      | 2150/125/1580/7.84           | 0.89 (0.75, 1.05)     |                   |
| Yes                             | 21621/89/477/18.60       | 5598/71/476/14.83            | 0.80 (0.65, 0.99)     |                   |

Figure 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.

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

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Disclosures

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Supplemental Material

Data S1

Tables S1–S17

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SUPPLEMENTAL MATERIAL
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.
| Abbreviation | Description               |
|--------------|---------------------------|
| 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.\textsuperscript{1,2} Restoring and maintaining sinus rhythm is associated with reduced mortality.\textsuperscript{3} Despite improved efficacy and safety of rhythm control therapy, previous trials have failed to demonstrate superiority over rate control.\textsuperscript{4–6} However, rhythm control therapy appears to be more effective when applied early.\textsuperscript{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\textsubscript{2}DS\textsubscript{2}-VASc-Score ≥2) to early rhythm control therapy or current guideline-based usual care.\textsuperscript{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.
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.
Patients diagnosed with AF between 7/28/2011 and 12/30/2016
N=

Patients without 12 months of enrollment prior to AF date
N=

Patients with at least 12 months of continuous enrollment prior to AF date
N=

Patients with AF diagnoses prior to AF date
N=

Patients with early AF
N=

- Patients who failed to meet the inclusion criteria
  N=
  - Patients who met at least one of the exclusion criteria
    N=
  - Invalid demographic or residence data
    N=

EAST group
Patients with early rhythm control therapy (AF ablation and/or any AAD) within the first year after AF date
N=

Usual care group
Patients without early rhythm control within the first year after AF date
N=
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. 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.\textsuperscript{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.\textsuperscript{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 $\leq 40\%$ 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/1.73m², and 90% of those who did not have a diagnosis had eGFR ≥60 mL/min/1.73m², 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: (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. 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 | Age >75 years, diagnosis codes for stroke or transient ischemic attack |
| 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 >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 |
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). The proportional hazards assumption will be tested on the basis of Schoenfeld residuals. 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.

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.\textsuperscript{30} The performance of IPTW often gets worse when the prevalence of treatment is low.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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, CHA2DS2-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. 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.\textsuperscript{35,37,38} We selected three endpoints 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.
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.
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### Table S1. List of Rhythm- and Rate-Control Drugs

| Rhythm-control drugs | Generic Names |
|----------------------|---------------|
| amiodarone, dofetilide, dronedarone, flecainide, propafenone, sotalol, quinidine, disopyramide, moricizine, procainamide, azimilide |

| Rate-control drugs | Beta Blockers | Calcium Blockers | Cardiac glycosides |
|-------------------|---------------|------------------|-------------------|
| atenolol, bisoprolol, carvedilol, metoprol, nadolol, nebivolol, propranolol, labetalol | diltiazem, verapamil | digoxin, digitoxin |
| Diagnosis Codes | Procedure Codes |
|----------------|----------------|
| Atrial Fibrillation | 427.31, 148.0, 148.1, 148.2, 148.91 |
| Catheter Ablation | 93651, 93656, 93657 |
| Ischemic stroke | 433.x1, 434.x1, 436, I63.x |
| Major bleeding | 456.0, 456.20, 530.21, 530.7, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 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, 538.0, 538.4, 538.6, 539.x1, K22.11, K22.6, K25.0, K25.1, K25.4, K25.6, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.4, K28.6, K29.x1, K31.81, 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, S06.35x, S06.36x, S06.37x, S06.38x, S06.4x, S06.5x, S06.6x |
| Other bleeding | 423.0, 459.0, 568.81, 596.7, I31.2, K66.1, M25.0, R04.1, S06.34x, S06.35x, S06.36x, S06.37x, S06.38x, S06.4x, S06.5x, S06.6x |

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            | Age >75 years, diagnosis codes for stroke or transient ischemic attack                                                                                                                                                        |
| 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 >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                                                                                                                                                                                                  |
| Criteria Number | Description                                                                                           | Codes or Details                                                                 |
|-----------------|-------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| 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   | AF diagnosis prior to index date                                                  |
|                 | escalation of therapy while on amiodarone                                                            |                                                                                  |
| 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       | Diagnosis codes for thyroid dysfunction                                            |
|                 | dysfunction, patients may be enrolled when their thyroid function is controlled.                      |                                                                                  |
| 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

| Region     | Before PS Weighting | After PS Weighting | p-value | Before | After | p-value |
|------------|---------------------|--------------------|---------|--------|-------|---------|
| 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   |
| Implant 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 |
| Characteristic                                      | Before | After | df  | p-value | Before | After | p-value |
|----------------------------------------------------|--------|-------|-----|---------|--------|-------|---------|
| 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

| Condition                                | Before PS Weighting | After PS Weighting | p-value |
|------------------------------------------|---------------------|--------------------|---------|
| Prior valve procedure                    | 2436 (2.9%)         | 2577 (9.5%)        | 0.274   |
| Mitral stenosis                          | 2114 (2.6%)         | 991 (3.7%)         | 0.063   |
| Mitral regurgitation                     | 33144 (40.1%)       | 13692 (50.5%)      | 0.210   |
| Major bleeding                           | 26015 (31.5%)       | 8241 (30.4%)       | 0.023   |
| Intracranial bleeding                    | 2995 (3.6%)         | 785 (2.9%)         | 0.041   |
| Stage 3-5 CKD                            | 16496 (20.0%)       | 4683 (17.3%)       | 0.069   |
| Renal failure requiring dialysis         | 1558 (1.9%)         | 414 (1.5%)         | 0.028   |
| Liver disease                            | 14697 (17.8%)       | 4674 (17.2%)       | 0.014   |
| Non skin cancer                          | 18294 (22.1%)       | 5494 (20.3%)       | 0.046   |
| Fall                                     | 19920 (24.1%)       | 4991 (18.4%)       | 0.139   |
| Anemia                                   | 48170 (58.3%)       | 15301 (56.4%)      | 0.037   |
| Alcoholism                               | 5589 (6.8%)         | 1771 (6.5%)        | 0.009   |
| Smocking                                 | 31269 (37.8%)       | 11296 (41.7%)      | 0.078   |
| Hypothyroidism                           | 27649 (33.5%)       | 8569 (31.6%)       | 0.039   |
| Thyrotoxicosis                           | 4734 (5.7%)         | 1379 (5.1%)        | 0.028   |
| Esophageal disease                       | 45830 (55.5%)       | 14450 (53.3%)      | 0.043   |
| Obesity                                  | 27124 (32.8%)       | 9998 (36.9%)       | 0.085   |
| COPD                                     | 20287 (24.6%)       | 6224 (23.0%)       | 0.037   |
| Obstructive sleep apnea                  | 17897 (21.7%)       | 7792 (28.7%)       | 0.164   |
| Hyperlipidemia                           | 72653 (87.9%)       | 23596 (87.1%)      | 0.026   |
| Osteoporosis                             | 18135 (21.9%)       | 4700 (17.3%)       | 0.116   |
Table S4. Baseline Characteristics Before and After PS Weighting in the Overall Cohort

|                                | Before PS Weighting | After PS Weighting | p-value |
|--------------------------------|---------------------|--------------------|---------|
| **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

|                      | Before PS Weighting | After PS Weighting | p-value | Before PS Weighting | After PS Weighting | p-value |
|----------------------|---------------------|--------------------|---------|---------------------|--------------------|---------|
| **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   |
| **CHA2DS2-VASc**     |                     |                    |         |                     |                    |         |
| Mean (SD)            | 4.7 (2.0)           | 4.3 (2.1)          | 0.224   | 4.7 (2.1)           | 4.7 (2.1)          | 0.000   |
| **CHA2DS2-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

|                | Before PS Weighting | After PS Weighting | p-value |
|----------------|---------------------|--------------------|---------|
| **2-3**        |                     |                    |         |
| Baseline period duration, years |                     |                    |         |
| Mean (SD)      | 4.9 (2.8)           | 5.1 (2.9)          | 0.000   |
| **4+**         |                     |                    |         |
| Health Utilization within past 12 months |                     |                    |         |
| Number of emergency room visits |                     |                    |         |
| Mean (SD)      | 0.8 (1.5)           | 0.9 (1.7)          | 0.000   |
| Number of inpatient stays |                     |                    |         |
| Mean (SD)      | 0.9 (1.2)           | 1.0 (1.5)          | 0.000   |
| Number of days in hospital |                     |                    |         |
| Mean (SD)      | 5.9 (12.0)          | 6.5 (14.5)         | 0.000   |
| Number of HF hospitalizations |                     |                    |         |
| Mean (SD)      | 0.1 (0.5)           | 0.2 (0.6)          | 0.000   |
| **Index year** |                     |                    |         |
| 2012           | 5216 (6.3%)         | 7185 (6.8%)        | 0.021   |
| 2013           | 14483 (17.5%)       | 1851 (18.2%)       | 0.018   |
| 2014           | 14168 (17.1%)       | 4273 (15.8%)       | 0.037   |
| 2015           | 13590 (16.4%)       | 4417 (16.3%)       | 0.004   |
| 2016           | 16629 (20.1%)       | 5440 (20.1%)       | 0.001   |
| 2017           | 18547 (22.4%)       | 6185 (22.8%)       | 0.009   |


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 CHA2DS2-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 |
| 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

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

| Drug                      | Before Weighting | After Weighting | p-value Before Weighting | p-value After Weighting |
|---------------------------|------------------|----------------|--------------------------|--------------------------|
| 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                  |
| **CHA2DS2-VASc**         |                  |                |                         |                          |                          |                       |
| Mean (SD)                | 4.9 (1.8)        | 4.6 (1.8)      | 0.203                    | 5.0 (1.8)                | 5.0 (1.8)                | 0.000                  |
| **CHA2DS2-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

| Year | Number of Emergency Room Visits (Mean (SD)) | Number of Inpatient Stays (Mean (SD)) | Number of Days in Hospital (Mean (SD)) | Number of HF Hospitalizations (Mean (SD)) | p-Value Before Weighting | p-Value After Weighting | p-Value Before Weighting | p-Value After Weighting | p-Value Before Weighting | p-Value After Weighting |
|------|---------------------------------------------|--------------------------------------|---------------------------------------|------------------------------------------|--------------------------|-------------------------|--------------------------|-------------------------|--------------------------|-------------------------|
| 2012 | 397 (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) before weighting, 0.8 (1.2) after weighting
  - p-Value: 0.068

- Number of inpatient stays
  - Mean (SD): 0.8 (1.1) before weighting, 1.2 (1.2) after weighting
  - p-Value: 0.370

- Number of days in hospital
  - Mean (SD): 5.0 (10.2) before weighting, 7.9 (11.9) after weighting
  - p-Value: 0.255

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 CHA2DS2-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

| Comorbidities          | Before Weighting | After Weighting | p-value  | Before Weighting | After Weighting | p-value  |
|------------------------|------------------|-----------------|----------|------------------|-----------------|----------|
| 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    |
| Condition                                | Before Weighting | After Weighting | Propensity Score | p-Value | Baseline | p-Value | Baseline | p-Value |
|------------------------------------------|------------------|-----------------|------------------|---------|----------|---------|----------|---------|
| Atrial flutter                           | 2346 (11.2%)     | 2387 (27.1%)    | 0.414            | 0.000   | 31.8%    | 0.000   | 31.8%    | 0.000   |
| Ventricular arrhythmia                   | 2983 (14.2%)     | 1449 (16.5%)    | 0.063            | 0.000   | 25.7%    | 0.000   | 25.7%    | 0.000   |
| Prior ablation for other arrhythmias     | 467 (2.2%)       | 1223 (13.9%)    | 0.439            | 0.000   | 36.1%    | 0.000   | 36.1%    | 0.000   |
| Cardioversion                           | 1440 (6.9%)      | 2617 (29.7%)    | 0.619            | 0.000   | 14.9%    | 0.000   | 14.9%    | 0.000   |
| Surgical ablation/Maze procedure         | 26 (0.1%)        | 117 (1.3%)      | 0.142            | 0.000   | 1.3%     | 0.000   | 1.3%     | 0.000   |
| Hypertension                            | 17960 (85.6%)    | 7081 (80.5%)    | 0.136            | 0.000   | 81.8%    | 0.000   | 81.8%    | 0.000   |
| Diabetes mellitus                       | 8119 (38.7%)     | 2611 (29.7%)    | 0.191            | 0.000   | 38.6%    | 0.000   | 38.6%    | 0.000   |
| Thromboembolism                         | 5436 (25.9%)     | 1657 (18.8%)    | 0.170            | 0.000   | 25.6%    | 0.000   | 25.6%    | 0.000   |
| Stroke                                  | 4524 (21.6%)     | 1280 (14.5%)    | 0.183            | 0.000   | 20.8%    | 0.000   | 20.8%    | 0.000   |
| Ischemic stroke                         | 3903 (18.6%)     | 1068 (12.1%)    | 0.180            | 0.000   | 18.4%    | 0.000   | 18.4%    | 0.000   |
| TIA                                     | 2817 (13.4%)     | 870 (9.9%)      | 0.110            | 0.000   | 12.6%    | 0.000   | 12.6%    | 0.000   |
| CAD                                     | 12574 (59.9%)    | 5414 (61.5%)    | 0.033            | 0.000   | 68.3%    | 0.000   | 68.3%    | 0.000   |
| PAD                                     | 4434 (21.1%)     | 1304 (14.8%)    | 0.165            | 0.000   | 21.7%    | 0.000   | 21.7%    | 0.000   |
| Vascular disease (CAD or PAD)           | 13138 (62.6%)    | 5533 (62.9%)    | 0.006            | 0.000   | 69.1%    | 0.000   | 69.1%    | 0.000   |
| Myocardial infarction                   | 5241 (25.0%)     | 1984 (22.5%)    | 0.057            | 0.000   | 33.2%    | 0.000   | 33.2%    | 0.000   |
| CABG                                    | 3206 (15.3%)     | 2067 (23.5%)    | 0.209            | 0.000   | 31.3%    | 0.000   | 31.3%    | 0.000   |
| PCI                                     | 3099 (14.8%)     | 1223 (13.9%)    | 0.025            | 0.000   | 22.0%    | 0.000   | 22.0%    | 0.000   |
| Left ventricular hypertrophy            | 7508 (35.8%)     | 3634 (41.3%)    | 0.114            | 0.000   | 44.9%    | 0.000   | 44.9%    | 0.000   |
| Prior valve procedure                   | 2436 (11.6%)     | 2577 (29.3%)    | 0.449            | 0.000   | 21.8%    | 0.000   | 21.8%    | 0.000   |
| Mitral stenosis                         | 2114 (10.1%)     | 991 (11.3%)     | 0.039            | 0.000   | 15.1%    | 0.000   | 15.1%    | 0.000   |
| Mitral regurgitation                    | 9157 (43.6%)     | 4842 (55.0%)    | 0.230            | 0.000   | 55.1%    | 0.000   | 55.1%    | 0.000   |
| Condition                                | Before Weighting | After Weighting | p-value | Before Weighting | After Weighting | p-value |
|------------------------------------------|------------------|-----------------|---------|------------------|-----------------|---------|
| 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 | Before Weighting | After Weighting | P-value |
|-------------------------|--------------------|------------------|----------------|---------|
|                         | 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 | Before Weighting | After Weighting | P-value |
|---------------------|------------------|----------------|---------|
| 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) | 4800 (22.9%) | 1957 (22.2%) | 0.015 | 24.3% | 24.3% | 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

| Category                                      | Before Weighting | After Weighting | P-value | Before Weighting | After Weighting | P-value |
|-----------------------------------------------|------------------|-----------------|---------|------------------|-----------------|---------|
| Calcium channel blockers (rate control)       |                  |                 |         |                  |                 |         |
| Other calcium channel blockers (not rate control) |                  |                 |         |                  |                 |         |
| Digitalis                                     | 2598 (12.4%)     | 801 (9.1%)      | 0.106   | 8.9%             | 8.9%            | 0.000   |
| Diuretics--aldosterone antagonist              | 3467 (16.5%)     | 1065 (12.1%)    | 0.126   | 10.6%            | 10.6%           | 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   |
| **CHA2DS2-VASc**                              |                  |                 |         |                  |                 |         |
| **Mean (SD)**                                 | 4.1 (2.5)        | 3.6 (2.4)       | 0.194   | 4.1 (2.5)        | 4.1 (2.5)       | 0.000   |
| **CHA2DS2-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 |
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 CHA2DS2-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                            |          |            |           |              |              |            | Absolute Rate         | Hazard Ratio          | P-value | P-value for interaction |
| <75 years                      | 17       | 1199       | 1.41      | 7            | 1236       | 0.58        | -0.83 (-1.44, -0.22)   | 0.42 (0.26, 0.68)     | <0.001   | 0.029                  |
| 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                         |          |            |           |              |              |            | Absolute Rate         | Hazard Ratio          | P-value |                         |
| Female                         | 16       | 876        | 1.79      | 14           | 888        | 1.52        | -0.27 (-1.15, 0.61)    | 0.89 (0.53, 1.50)     | 0.665    | 0.123                  |
| 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                           |          |            |           |              |              |            | Absolute Rate         | Hazard Ratio          | P-value |                         |
| Non-white                      | 12       | 450        | 2.61      | 7            | 476        | 1.39        | -1.22 (-2.64, 0.20)    | 0.54 (0.29, 1.01)     | 0.055    | 0.469                  |
| 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    |                        |
| CHA2DS2-VASc                   |          |            |           |              |              |            | Absolute Rate         | Hazard Ratio          | P-value |                         |
| 0-1                            | 1        | 158        | 0.49      | 0            | 170        | 0.03        | -0.46 (-1.38, 0.47)    | 0.07 (0.01, 0.77)     | 0.030    | 0.147                  |
| 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   |          |            |           |              |              |            | Absolute Rate         | Hazard Ratio          | P-value |                         |
| 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    | 0.653                  |
| 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                    |          |            |           |              |              |            | Absolute Rate         | Hazard Ratio          | P-value |                         |

Note: P-values for interaction are based on comparing the hazard ratios across subgroups.
Table S7. Subgroup Analysis for the Secondary Outcome Stroke in Propensity Score Weighted Patients (Overall Cohort)

|                          | No prior SHF | Prior SHF | No prior CM | Prior CM | Cardiomyopathy | No prior CM | Prior CM | Obstructive Sleep Apnea | No prior OSA | Prior OSA | Thromboembolism | No prior TE | Prior TE |
|--------------------------|--------------|-----------|-------------|----------|----------------|-------------|----------|--------------------------|--------------|-----------|-------------------|------------|----------|
|                          | 28           | 1708      | 17          | 1661     | 1.00           | -0.64 (-1.23, -0.06) | 0.62 (0.42, 0.92) | 0.017 |
| Prior SHF                | 9            | 477       | 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      | 15          | 1548     | 0.99           | -0.58 (-1.18, 0.02)  | 0.65 (0.43, 0.99) | 0.043 |
| Prior CM                 | 13           | 657       | 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      | 20          | 1622     | 1.26           | -0.50 (-1.13, 0.13)  | 0.73 (0.49, 1.08) | 0.117 |
| Prior OSA                | 9            | 577       | 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      | 14          | 1675     | 0.85           | -0.42 (-0.94, 0.10)  | 0.68 (0.43, 1.07) | 0.092 |
| Prior TE                 | 16           | 523       | 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 | P-value | P-value for interaction |
| Age                            |          |               |          |          |               |          |          |                     |
| <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                         |          |               |          |          |               |          |          |                     |
| 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       | 1270          | 4.08     | 47       | 1261          | 3.70     | -0.38 (-1.51, 0.75) | 0.90 (0.68, 1.20) | 0.482 |
| Race                           |          |               |          |          |               |          |          |                     |
| 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       | 1700          | 3.41     | 59       | 1665          | 3.54     | 0.12 (-0.78, 1.03)  | 1.05 (0.81, 1.36) | 0.739 |
| CHA2DS2-VASc                   |          |               |          |          |               |          |          |                     |
| 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       | 1503          | 5.38     | 76       | 1505          | 5.03     | -0.35 (-1.55, 0.85) | 0.95 (0.76, 1.18) | 0.625 |
| Left Ventricular Hypertrophy   |          |               |          |          |               |          |          |                     |
| 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                    |          |               |          |          |               |          |          |                     |


| Subgroup Analysis | No prior SHF | Prior HF | Cardiomyopathy | No prior CM | Prior CM | Obstructive Sleep Apnea | No prior OSA | Prior OSA | Thromboembolism | No prior TE | Prior TE |
|-------------------|-------------|---------|----------------|-------------|---------|-------------------------|-------------|----------|----------------|-----------|---------|
|                   | 33 | 1698 | 1.95 | 27 | 1647 | 1.64 | -0.31 (-0.95, 0.33) | 0.85 (0.60, 1.19) | 0.338 |
| Cardiomyopathy    | 51 | 428 | 11.82 | 51 | 477 | 10.76 | -1.06 (-4.34, 2.22) | 0.95 (0.72, 1.26) | 0.729 |
|                   | 47 | 1497 | 3.16 | 32 | 1526 | 2.08 | -1.08 (-1.95, -0.21) | 0.67 (0.49, 0.90) | 0.009 |
|                   | 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 | 56 | 1570 | 3.54 | 54 | 1579 | 3.39 | -0.15 (-1.08, 0.78) | 0.97 (0.75, 1.27) | 0.848 |
|                   | 28 | 5,56 | 5.07 | 25 | 544 | 4.56 | -0.51 (-2.46, 1.44) | 0.89 (0.60, 1.32) | 0.556 |
| Thromboembolism   | 55 | 1614 | 3.44 | 52 | 1627 | 3.21 | -0.23 (-1.15, 0.69) | 0.94 (0.72, 1.23) | 0.641 |
|                   | 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)

| Variable                  | Control | Early Rhythm-Control | P-value | P-value for interaction |
|---------------------------|---------|----------------------|---------|-------------------------|
|                           | No. of Events | Person Years | Event Rate | No. of Events | Person Years | Event Rate | Absolute Rate Difference (95% CI) | Hazard Ratio (95% CI) |                         |
| Age                       |          |                     |          |              |              |           |                                      |                          |                          |
| <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                    |          |                     |          |              |              |           |                                      |                          |                          |
| 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                      |          |                     |          |              |              |           |                                      |                          |                          |
| 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                    |
| CHA2DS2-VASc              |          |                     |          |              |              |           |                                      |                          |                          |
| 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 |            |                     |          |              |              |           |                                      |                          |                          |
| 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               |          |                     |          |              |              |           |                                      |                          |                          |
Table S9. Subgroup Analysis for the Secondary Outcome Hospitalization with the Diagnosis Myocardial Infarction in Propensity Score Weighted Patients (Overall Cohort)

| Condition                  | No prior | N  | CI  | N  | CI  | p-value |
|----------------------------|----------|----|-----|----|-----|---------|
| SHF                        |          |    |     |    |     |         |
| Prior                      | 9        | 481| 1.78| 8  | 530 | 1.55    | 0.778   |
| Prior CM                   | 7        | 667| 1.03| 11 | 636 | 1.80    | 0.114   |
| Prior OSA                  | 10       | 581| 1.75| 6  | 565 | 1.03    | 0.098   |
| Prior TE                   | 13       | 526| 2.53| 9  | 514 | 1.76    | 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 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                   |
| CHA2DS2-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)

| Subgroup | No prior SHF | Prior HF | Cardiomyopathy | Obstructive Sleep Apnea | Thromboembolism |
|----------|--------------|----------|-----------------|--------------------------|-----------------|
|          | 79 | 1754 | 4.52 | 66 | 1683 | 3.92 | -0.60 (-1.55, 0.36) | 0.87 (0.70, 1.09) | 0.225 |
|          | 61 | 489 | 12.40 | 56 | 540 | 10.36 | -2.04 (-4.94, 0.86) | 0.82 (0.64, 1.05) | 0.116 |
| 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 |
| 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 |
| 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)

| Age                | 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 |                          |                        |                      |                      |                      |
| <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             |                |              |            |              |              |            |                          |                        |                      |                      |
| 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               |                |              |            |              |              |            |                          |                        |                      |                      |
| Non-white          | 38           | 284          | 13,29      | 32           | 316          | 10,07       | -3.22 (-7.29, 1.05)       | 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                |                      |
| CHA2DS2-VASc       |                |              |            |              |              |            |                          |                        |                      |                      |
| 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 |            |              |            |              |              |            |                          |                        |                      |                      |
| 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)

|                  | SHF       | Apnea     | CM        | OSA       | TE        |
|------------------|-----------|-----------|-----------|-----------|-----------|
| 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**                  |               |                |            |               |                |            |                             |                       |                      |
| <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**               |               |                |            |               |                |            |                             |                       |                      |
| 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**                 |               |                |            |               |                |            |                             |                       |                      |
| 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                |
| **CHA2DS2-VASc**         |               |                |            |               |                |            |                             |                       |                      |
| 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** |           |                |            |               |                |            |                             |                       |                      |
| 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                |
|                  | Systolic HF | 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                  | Absolute Rate Difference (95% CI) | Hazard Ratio (95% CI) | P Value |
|-------------------------------------|--------------------------------------|---------------------------------------|----------------------------------|-----------------------|---------|
| Overall cohort - with AF ablation   |                                      |                                       |                                  |                       |         |
| Total                               | N=82,633                             | N=2470                                | -1.05 (-2.84, 0.75)              | 0.80 (0.55, 1.18)     | 0.261   |
| Composite                           | 33                                   | 26                                    | 5.40                             | 4.36                  |         |
| Stroke                              | 5                                    | 4                                     | 0.76                             | 0.64                  | -0.12 (-0.80, 0.57) | 0.87 (0.32, 2.39) | 0.786   |
| HF                                  | 12                                   | 14                                    | 1.94                             | 2.44                  | 0.50 (-0.79, 1.78)  | 1.27 (0.72, 2.23) | 0.409   |
| MI                                  | 5                                    | 3                                     | 0.81                             | 0.46                  | -0.35 (-0.89, 0.18) | 0.57 (0.24, 1.37) | 0.209   |
| Mortality                           | 19                                   | 14                                    | 3.05                             | 2.26                  | -0.79 (-2.09, 0.50) | 0.74 (0.44, 1.24) | 0.250   |
| Overall cohort - without AF ablation (AAD only) |                                      |                                       |                                  |                       |         |
| Total                               | N=82,633                             | N=24,636                              | -1.89 (-3.87, 0.10)              | 0.86 (0.74, 1.00)     | 0.048   |
| Composite                           | 177                                  | 154                                   | 13.28                            | 11.39                 | -1.89 (-3.87, 0.10) | 0.86 (0.74, 1.00) | 0.048   |
| Stroke                              | 29                                   | 18                                    | 2.00                             | 1.23                  | -0.77 (-1.46, -0.07) | 0.62 (0.43, 0.90) | 0.013   |
| HF                                  | 65                                   | 58                                    | 4.67                             | 4.14                  | -0.53 (-1.70, 0.63) | 0.89 (0.70, 1.15) | 0.388   |
| MI                                  | 25                                   | 21                                    | 1.74                             | 1.48                  | -0.27 (-0.94, 0.41) | 0.86 (0.58, 1.27) | 0.440   |
| Mortality                           | 110                                  | 99                                    | 7.42                             | 6.71                  | -0.71 (-2.09, 0.68) | 0.91 (0.75, 1.10) | 0.323   |
| Eligible for Trial -with AF ablation |                                      |                                       |                                  |                       |         |
| Total                               | N=61,641                             | N=1543                                | -0.65 (-3.09, 1.78)              | 0.89 (0.58, 1.35)     | 0.583   |
| Composite                           | 26                                   | 21                                    | 6.16                             | 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 | HF    | MI    | Mortality | Eligible for Trial -without AF ablation (AAD only) | N=61,641 |                 | N=16,764 |                 |
|------------------|--------|-------|-------|-----------|---------------------------------------------------|----------|----------------|----------|-----------------|
|                  |        |       |       |           | Composite                                         | 129      | 1,023          | 1.25     | 110             |
|                  |        |       |       |           | Stroke                                            | 24       | 1,093          | 1.09     | 14             |
|                  |        |       |       |           | HF                                                | 43       | 1,064          | 0.99     | 40             |
|                  |        |       |       |           | MI                                                | 20       | 1,104          | 0.77     | 15             |
|                  |        |       |       |           | Mortality                                         | 82       | 1,127          | 0.72     | 68             |
| Stroke           | 4      | 439   | 0.95  | 406       | 0.96                                             | 0.01     | (-0.98, 1.01)  | 1.05     |
| HF               | 8      | 437   | 1.91  | 394       | 2.85                                             | 0.95     | (-0.72, 2.62)  | 1.48     |
| MI               | 4      | 442   | 0.99  | 408       | 0.63                                             | -0.36    | (-1.11, 0.39)  | 0.63     |
| Mortality        | 16     | 447   | 3.57  | 413       | 2.61                                             | -0.96    | (-2.66, 0.75)  | 0.74     |
|                  |        |       |       |           | Composite                                         | 129      | 1,023          | 1.25     | 110             |
|                  |        |       |       |           | Stroke                                            | 24       | 1,093          | 1.09     | 14             |
|                  |        |       |       |           | HF                                                | 43       | 1,064          | 0.99     | 40             |
|                  |        |       |       |           | MI                                                | 20       | 1,104          | 0.77     | 15             |
|                  |        |       |       |           | Mortality                                         | 82       | 1,127          | 0.72     | 68             |
| Eligible for Trial -without AF ablation (AAD only) | N=61,641 |                 | N=16,764 |                 |
|                  |        |       |       |           | Composite                                         | 129      | 1,023          | 1.25     | 110             |
|                  |        |       |       |           | Stroke                                            | 24       | 1,093          | 1.09     | 14             |
|                  |        |       |       |           | HF                                                | 43       | 1,064          | 0.99     | 40             |
|                  |        |       |       |           | MI                                                | 20       | 1,104          | 0.77     | 15             |
|                  |        |       |       |           | Mortality                                         | 82       | 1,127          | 0.72     | 68             |
| Ineligible for Trial -with AF ablation | N=20,992 |                 | N=927 |                 |
|                  |        |       |       |           | Composite                                         | 6        | 180            | 0.31     | 0              |
|                  |        |       |       |           | Stroke                                            | 1        | 186            | 0.31     | 0              |
|                  |        |       |       |           | HF                                                | 4        | 181            | 0.20     | 3              |
|                  |        |       |       |           | MI                                                | 1        | 185            | 0.38     | 0              |
|                  |        |       |       |           | Mortality                                         | 3        | 186            | 1.81     | 3              |
|                  |        |       |       |           | Composite                                         | 49       | 311            | 15.62    | 44             |
|                  |        |       |       |           | Stroke                                            | 4        | 347            | 1.23     | 4              |
| Ineligible for Trial -without AF ablation (AAD only) | N=20,992 |                 | N=7872 |                 |
|                  |        |       |       |           | Composite                                         | 49       | 311            | 15.62    | 44             |
|                  |        |       |       |           | Stroke                                            | 4        | 347            | 1.23     | 4              |
### Table S13. Sensitivity Analyses Stratified by Treatment with AF Ablation or without AF Ablation in the Early Rhythm-Control Therapy Cohort

|        | HF  | 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)

| Event                  | Control                  | Early Rhythm-Control          | Absolute Rate Difference (95% CI) | Hazard Ratio (95% CI) | P Value |
|------------------------|--------------------------|-------------------------------|----------------------------------|-----------------------|---------|
|                        | No. of Events | Person Years | Event Rate | No. of Events | Person Years | Event Rate |                     |           |
| 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          | Absolute Rate Difference (95% CI) | Hazard Ratio (95% CI) | P Value |
|------------------|--------------------------------|-------------------------------|-----------------------------------|----------------------|---------|
|                  | No. of Events | Person Years | Event Rate | No. of Events | Person Years | Event Rate |                                      |          |         |
| 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        | Absolute Rate Difference (95% CI) | Hazard Ratio (95% CI) | P Value |
|--------------------------|-----------------------|-----------------------------|----------------------------------|-----------------------|---------|
|                          | No. of Events | Person Years | Event Rate | No. of Events | Person Years | Event Rate |                        |                        |         |
| **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.