SUPPLEMENTAL MATERIAL

DATA S1. STATISTICAL ANALYSIS PLAN

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

ABBREVIATIONS

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

Key Definition

First AF Date (variable name first_AF_date)

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

Index Date (variable name index_date)

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

Baseline Period (variable name baseline)

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

Study Period

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

Early Rhythm Control Therapy

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

BACKGROUND AND OBJECTIVES

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

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

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

STUDY DESIGN AND DATA SOURCE

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

STUDY POPULATION

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

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

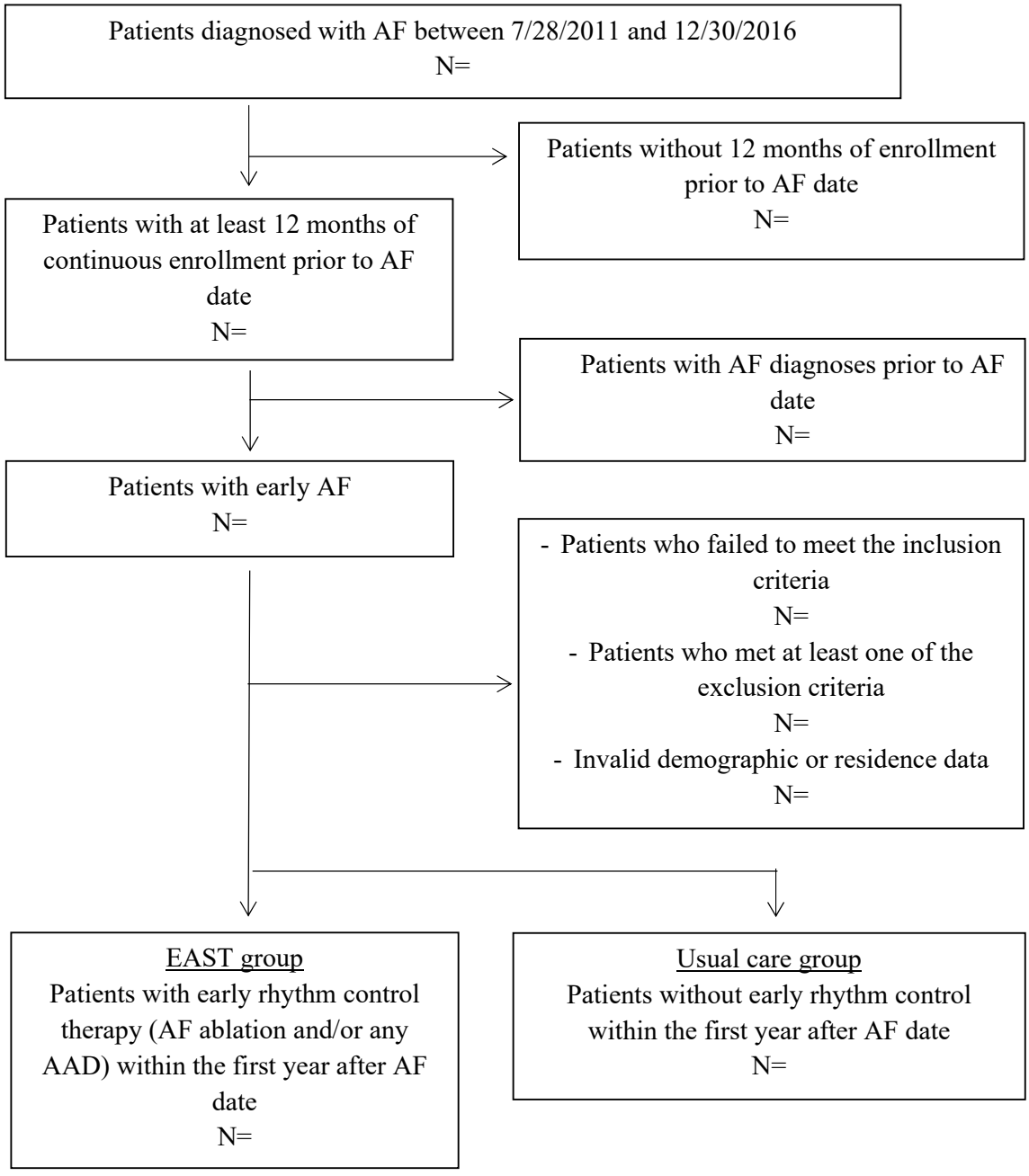
We will then limit to those who were older than 75 years of age or had had a previous transient ischemic attack or stroke, or met two of the following criteria: age greater than 65 years, female sex, heart failure, hypertension, diabetes mellitus, severe coronary artery disease, chronic kidney disease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

Table 1. Generic Names of Anti-Arrhythmic Drug Therapy

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

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

Figure 1. Patients Selection Flow Diagram



MEASUREMENTS

Baseline Characteristics

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

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

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

Follow up and Outcomes

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

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

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

Missing Data

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

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

Internal Validation of Diagnosis Codes

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

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

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

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

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

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

STATISTICAL METHODS

Main Analyses

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

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

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

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

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

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

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

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

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

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

Propensity Score Methods

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

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

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

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

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

Sensitivity Analyses

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

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

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

Subgroup Analyses

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

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

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

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

Residual Confounding

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

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

LIMITATIONS

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

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

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

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

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

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

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

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

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

Table S3. EAST-AFNET 4 Trial Eligibility Criteria

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

Table S3. EAST-AFNET 4 Trial Eligibility Criteria

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table S17. Falsification Endpoint Test in Propensity Score Weighted Cohort

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

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