**Comparative Effectiveness of Early Rhythm Control Versus Rate Control for Cardiovascular Outcomes in Patients with Atrial Fibrillation**

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**ABSTRACT**

**Background:** Rhythm control is associated with better cardiovascular outcomes than usual care among patients recently diagnosed with atrial fibrillation (AF).

**Objective:** To investigate the effects of rhythm control compared to rate control on the incidence of stroke, heart failure (HF), myocardial infarction, and cardiovascular death stratified by timing of treatment initiation.

**Methods:** We conducted a retrospective population-based cohort study including 22635 patients with AF newly treated with rhythm control (antiarrhythmic drugs or ablation) or rate control in 2011-2015 from the Korean National Health Insurance Service database. Propensity overlap weighting was used to compare the outcomes.

**Results:** Compared to rate control, rhythm control initiated within 16 months of AF diagnosis decreased the risk of stroke. The point estimates for rhythm control initiated at selected time points after AF diagnosis compared to rate control are as follows; 1 year, hazard ratio (HR) 0.78 (95% confidence interval [CI] 0.66-0.93) and 5 years, HR 1.00 (95% CI 0.45-2.24). Compared with rate control, the initiation of rhythm control within 7 months of AF diagnosis reduced the risk of hospitalization for HF: 6 months, HR 0.84 (95% CI 0.74–0.95) and 5 years, HR 2.88 (95% CI 1.34–6.17). The risks of myocardial infarction and cardiovascular death did not differ between rhythm and rate control regardless of treatment timing.

**Conclusions:** Early initiation of rhythm control was associated with a lower risk of stroke and HF-related admission than rate control in patients with recently diagnosed AF. The effect were attenuated as initiating the rhythm control treatment later.

**Keywords:** atrial fibrillation; rhythm control; rate control; cardiovascular outcome.

**Introduction**

Atrial fibrillation (AF) increases the risk of mortality and morbidity due to stroke and congestive heart failure (HF) and impairs the quality of life.1-3 Treatment strategies for AF are broadly characterised into two categories: rhythm-control strategy, to maintain sinus rhythm, and rate-control strategy, to reduce the ventricular rate. Previous randomized trials comparing rhythm-control and rate-control strategies, including the landmark Atrial Fibrillation Follow-up Investigation of Sinus Rhythm Management (AFFIRM) trial, have reported no significant differences between the treatment strategies with respect to mortality and stroke incidence.4-6 Similarly, a meta-analysis of five randomized trials comparing the rhythm-control strategy with the rate-control strategy indicated no significant differences of the risk for all-cause mortality, although the results appeared to favor the rate-control strategy.7

By contrast, recent studies have revealed that rhythm control is associated with a lower risk of adverse cardiovascular outcomes than usual care among patients with recently (within 1 year) diagnosed AF.8,9 The Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4) trial revealed that patients randomly assigned to receive early rhythm control had a low risk of death due to cardiovascular causes, stroke, and hospitalization for the worsening of HF or acute coronary syndrome, as well as a low risk of individual components of death due to cardiovascular causes and stroke.8 Kim et al. assessed data from the Korean National Health Insurance Service (NHIS) database and reported that rhythm control was associated with a lower risk of composite cardiovascular outcomes than rate control in patients with recently diagnosed AF; however, this finding was not observed in patients who had experienced AF for more than 1 year. Principally, a restored and maintained sinus rhythm with reduced AF burden is expected to reduce the risk of stroke, HF, and other cardiovascular outcomes and result in a good prognosis.10,11 However, how early should we start rhythm control and which individual cardiovascular outcomes are improved by the early rhythm control are unclear. This study examined the comparative effectiveness of rhythm control versus rate control on cardiovascular outcomes stratified by the timing of treatment initiation.

**Methods**

 This retrospective study was based on the National Health Claims Database established by the NHIS of Korea. Further details are presented in Supplemental Methods. This study was approved by the Institutional Review Board of the Yonsei University Health System (4-2016-0179).

*Cohort design and study population*

This study emulated a randomized controlled trial comparing the effect of rhythm- versus rate-control treatment for AF on the risk of cardiovascular outcomes. The details of the trial protocol are presented in Supplemental Table S1. We identified adults (age: ≥18 years) with AF who were treated with rhythm- or rate-control strategies between July 28, 2011 and December 31, 2015 and who were older than 75 years of age, had a history of a transient ischemic attack (TIA) or stroke, or met two of the following criteria: age > 65 years, female sex, HF, hypertension, diabetes mellitus, previous myocardial infarction, or chronic kidney disease, using a similar inclusion period and criteria as the EAST-AFNET 4 trial.8 AF was defined according to the International Classification of Disease, 10th Revision (ICD-10) code I48. The diagnosis of AF has been previously validated in the NHIS database with a positive predictive value of 94.1%.12 We used a new-user and intention-to-treat design for rhythm- or rate-control treatments. New users were defined as those with no previous records of prescriptions or procedures of interest in the database. Intention to treat with rhythm control was defined as a prescription of more than a 90-day supply of any rhythm-control drugs in the 180-day period since the first prescription or performance of an ablation procedure for AF. Intention-to-treat with rate control was defined as a prescription of more than a 90-day supply of any rate-control drugs in the 180-day period since the first prescription, with no prescriptions of rhythm-control drugs and ablation within this period. Patients who were prescribed rhythm-control drugs for more than 90 days or who underwent ablation within the 180-day period since the initiation of rate-control drugs were classified into the intention-to-treat with rhythm control group (N=8,350). Rhythm- and rate-control drugs and claim codes for ablation procedures are presented in Supplemental Table S2. This study excluded patients without a prescription of more than a 90-day supply of warfarin or a direct oral anticoagulant within the 180-day period since the initiation of rhythm- or rate-control drugs or the performance of an ablation procedure for AF and those who died within 180 days of the first record of a prescription or procedure (Figure 1A).

*Outcome and Covariates*

We investigated the individual components of the primary composite outcome of the EAST-AFNET 4 trial: ischemic stroke, hospitalization due to HF, acute myocardial infarction, and cardiovascular death. Detailed definitions of the outcomes are presented in Supplemental Table S3. The study outcomes were followed-up from 180 days after the first recorded prescription or procedure until the end of follow-up (December 31, 2016) or death. Details about covariates are presented in Supplemental Methods and Supplemental Table S2.

*Statistical methods*

Descriptive statistics were used to describe baseline characteristics. Overlap weighting based on a propensity score was used to assess the differences in baseline characteristics between the rhythm-control and rate-control groups. The propensity score, which represents the probability of receiving rhythm control, was estimated using logistic regression based on socio-demographic factors, time from AF diagnosis, year of therapy initiation, level of care at which the prescription was provided, clinical risk scores, medical history, and concurrent medication use (variables in Table 1). Continuous variables were modelled as cubic spline functions. The distribution of propensity scores before and after overlap weighting is shown in Supplemental Figure S1. The overlap weight was calculated as 1 minus the propensity score for patients who received rhythm control, and as the propensity score for patients who received rate control, to obtain estimates representing the average treatment effects in the population with a minimised asymptotic variance of the treatment effect and desirable exact balance property.13 The balance between the treatment populations was evaluated by standardized differences of all baseline covariates using a threshold of 0.1 to indicate imbalance. Competing risk regression by Fine and Gray was used to consider all-cause death as a competing event when estimating the relative hazards of clinical outcomes.14 Cofactors that had not been balanced by weighting were included as covariates in the competing risk regression. The proportional hazards assumption was tested based on Schoenfeld residuals.To explore the treatment timing–dependent effect of rhythm control on the cardiovascular outcomes, Cox proportional-hazards models were fit to the entire weighted study population using an interaction term for treatment timing after AF diagnosis (modelled as a natural spline) and treatment (rhythm-control or rate-control strategy). Standard errors were computed using 1000 bootstrap replicates. Two-sided P-values of <0.05 were considered significant. Statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC, USA) and R version 3.6.0 (The R Foundation, www.R-project.org).

*Sensitivity analyses*

Firstly, we performed analyses in analogy to the on-treatment principle by censoring patients who switched to another treatment strategy or discontinued their treatment (censored at the time of switch or discontinuation). Secondly, one-to-one propensity score matching (without replacement with a calliper of 0.01) was used instead of overlap weighting. The balance of covariates after matching is shown in Supplemental Table S4. Thirdly, we performed “falsification analysis” to measure systematic bias in this study by employing 45 pre-specified falsification endpoints, with true hazard ratios of 1.Detailed definitions of the falsification endpoints are presented in Supplemental Table S5.

**Results**

*Patient characteristics*

In total, 9,246 of 13,653 (67.7%) patients started receiving rhythm-control therapy within 1 year of AF diagnosis (early rhythm control). In contrast, 7,077 of 8,982 (78.8%) patients started receiving rate-control therapy within 1 year of AF diagnosis (early rate control) (Table 1). The most commonly used rhythm-control drug was the class III drug amiodarone (40.4%), followed by class Ic drugs (Figure 1B). Ablation was the initial rhythm-control strategy in 5.7% and was eventually performed during follow-up in 11.0% of the patients in the rhythm-control group.

Patients in the rhythm-control group were more likely to have comorbidities such as hypertension, diabetes, vascular disease, and chronic kidney disease and less likely to have a history of HF-related admission and ischemic stroke than patients in the rate-control group. After overlap weighting, all baseline characteristics were similar between the two groups (Table 1).

*Stroke*

During the mean follow-up of 2.3±1.3 years, 1419 patients experienced stroke: 715 (5.2%) in the rhythm-control group and 704 (7.8%) in the rate-control group. The rhythm-control strategy was associated with a reduction in stroke incidence compared with the rate-control strategy (2.80 vs. 3.65 events per 100 person-years; hazard ratio [HR] 0.77, 95% confidence interval [CI] 0.65–0.92, P=0.004) (Figure 2). The rhythm-control strategy was consistently associated with a reduction in stroke incidence compared with the rate-control strategy in on-treatment analysis and after propensity score matching (Figure 2). The weighted cumulative incidence curves showed that the cumulative incidence of stroke was significantly lower in the rhythm-control group than in the rate-control group (log-rank P<0.001) (Figure 3A).

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

*HF-related hospitalization*

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

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

*Other outcomes and falsification endpoints*

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

In the analyses of 45 falsification endpoints, the 95% CIs of the associations of rhythm-control with each endpoint covered one in 45 (100%) endpoints (Supplemental Table S6).

**Discussion**

 In this study, the initiation of rhythm control, rather than that of rate control, within 16 months of AF diagnosis was associated with a decreased risk of ischemic stroke. The initiation of rhythm control within 7 months of AF diagnosis was associated with a decreased risk of HF-related hospitalization. Furthermore, no differences were found in the incidence of acute myocardial infarction and cardiovascular death between the two groups, regardless of the timing of treatment.

*Lower risks of stroke and HF hospitalization by early rhythm control*

In the EAST-AFNET 4 trial, early rhythm control lowered the risk of stroke by 35% compared with usual care.8 Consistently, Kim et al. reported that the risk of stroke can be 26% decreased by early rhythm-control therapy rather than by rate-control therapy.9 In this study, rhythm control was associated with less frequent stroke events and a lower risk of stroke when initiated within 16 months of AF diagnosis. This result is in line with that of a post-hoc analysis of the ATHENA trial, which demonstrated that dronedarone use was associated with a significant reduction in the risk of ischemic and hemorrhagic stroke.15 In population-based observational cohort studies, rhythm control with antiarrhythmic drugs or catheter ablation was associated with lower rates of stroke/TIA than rate-control therapy.11,16

In the EAST-AFNET 4 trial, early rhythm control showed a trend of reduction in the incidence of hospitalization for worsening of HF, without statistical significance.8 Kim et al. assessed real-world data and reported that early rhythm control might be associated with a reduction in the risk of hospitalization for HF.9 In this study, rhythm control was associated with a lower risk of hospitalization for HF when initiated within 7 months of AF diagnosis. A large US cohort study reported that patients with AF who undergo ablation have a significantly lower risk of long-term HF than those who do not undergo ablation.17 In a randomized-controlled trial, catheter ablation for AF was associated with significantly lower rates of a composite endpoint of all-cause death and hospitalization for worsening HF in patients with HF and reduced ejection fraction.18 The association between antiarrhythmic drug treatment and HF is not well known. However, dronedarone use was associated with a decreased incidence of hospitalization for HF in the ATHENA trial, without statistical significance, owing to the small number of events.15 In contrast, the results of the Permanent Atrial fibriLLAtion outcome Study (PALLAS) using dronedarone in addition to standard therapy indicated that dronedarone use increased the rates of HF, stroke, and death due to cardiovascular causes in patients with permanent AF at risk for major vascular events.19 Consistently, we observed trends in favor of the rate-control strategy when therapy initiation was delayed.

The association between early rhythm control and lower cardiovascular mortality in this study was less prominent than that in the EAST-AFNET 4 trial, which might be explained by a relatively shorter follow-up period (median: 2.5 vs. 5.1 years in the EAST-AFNET 4 trial).The association between early rhythm control and acute myocardial infarction has not been observed in previous studies.8,9

*Mechanism*

Precise mechanisms by which early rhythm control confers benefits were not assessed in this clinical observational study; however, early rhythm control may be associated with an early impact on electrical and substrate remodelling.21 In addition, patients receiving rhythm control may have had a more careful, structured follow-up; however, in that case, we would have observed benefits in both the early and late rhythm-control subgroups. Contemporary rhythm-control treatments use antiarrhythmic drugs that are better tolerated and safer than those used (i.e. class Ia agents) in trials comparing rate-control versus rhythm-control strategies 2–3 decades ago.6 Yang et al. reported that no difference in survival, cardiovascular hospitalization incidence, or ischemic stroke incidence was found between patients diagnosed with AF within 6 months of study enrolment who were treated with rate control and rhythm control in the AFFIRM trial.22 In addition, they concluded that the superiority of the rhythm-control strategy reported in recent AF trials may be more attributable to the refinement of AF therapies and less related to the timing of intervention. Although rhythm control included all major antiarrhythmic drugs and ablation in this study, both dronedarone and ablation are not popular choices for treatment of AF (dronedarone, 1.9%; ablation, 5.7%) (Figure 1B). These findings suggest that the favorable outcomes of rhythm control, which were only observed in AF patients who started treatment shortly after diagnosis, could not be fully explained by the use of a promising drug or ablation, which may not have been available in previous trials, and might be associated with the timing of treatment.

*Study limitations*

The present study has several limitations. In this study, data from a claims-based database were used; hence, the burden of AF (rhythm status) was not evaluated. Thus, the role of AF burden, a contributor to outcomes, remains unknown. We defined AF diagnoses and ablation cases using only ICD-10 or claim codes, and therefore, data regarding AF type (paroxysmal vs. non-paroxysmal) or symptoms (symptomatic vs. asymptomatic) were not available. The findings from this observational study cannot be used to establish causal relationships, and residual confounding may persist even after propensity score weighting or matching. However, the results of the falsification analysis revealed that the presence of significant systematic bias was less likely. We were unable to determine the exact reasons for the selection of the rhythm-control strategy over the rate-control strategy, which may introduce potential bias, and the unmeasured confounders (quality of anticoagulation therapy and lifestyle factors such as obesity, alcohol intake, and physical activity) may have influenced the findings. Nonetheless, we identified sufficient overlap of propensity scores between the groups, which represents the existence of equipoise between the two therapies. Because of the active-comparator design of this study, asymptomatic patients with AF who did not require therapy may have been excluded. In addition, owing to the new-user design, in according to which prevalent drug users at the time of AF diagnosis were excluded, the proportions of treatment strategies selected for patients with AF in this study may not fully reflect the preferences in real-world clinical practice*.*

**Conclusions**

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

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**Figure 1.** (A) Flowchart of the enrolment and analysis of the study population and (B) initial choice of rhythm-control treatments. \*Patients prescribed rhythm control drugs for more than 90 days or those who underwent ablation within the 180 day period since the initiation of rate control drugs were classified as intention to treat with rhythm control.

AF, atrial fibrillation.

**Figure 2.** Cardiovascular outcomes in patients receiving rhythm- and rate-control treatments.

Event rates are per 100 person-years.

\*Incidences and hazard ratios are overlap weighted.

CI, confidence interval.

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

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

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

**Figure 5.** Point estimates of rhythm control compared with rate control for cardiovascular outcomes according to timing of treatment initiation.

AF; atrial fibrillation. Values are presented as hazard ratios (95% confidence intervals).

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

CI, confidence interval; HR, hazard ratio.

**Table 1.** Baseline characteristics of patients receiving rhythm- and rate-control treatments before and after overlap weighting.

|  |  |  |
| --- | --- | --- |
|  | **Before overlap weighting** | **After overlap weighting** |
| **Variables** | RhythmControl(N=13653) | RateControl(N=8982) | ASD | RhythmControl(N=13653) | RateControl(N=8982) | ASD |
| **Sociodemographic** |  |  |  |  |  |  |
| Age, years  | 68 (60-75) | 72 (64-78) | 25.5% | 70 (62-76) | 71 (62-77) | <0.1% |
| <65 years | 4795 (35.1) | 2334 (26.0) | 19.9% | 29.7 | 29.7 | <0.1% |
| 65-74 year | 5279 (38.7) | 3160 (35.2) | 7.2% | 37.1 | 37.1 | <0.1% |
| ≥75 years | 3579 (26.2) | 3488 (38.8) | 27.2% | 33.1 | 33.1 | <0.1% |
| Male | 7364 (53.9) | 4836 (53.8) | 0.2% | 54.7 | 54.7 | <0.1% |
| AF duration, months | 1.3 (0.0-31.5) | 0.0 (0.0-5.3) | 28.2% | 0.6 (0.0-13.6) | 0.1 (0.0-14.7) | <0.1% |
| Early AF (initiating treatment within 1 year after diagnosis) | 9246 (67.7) | 7077 (78.8) | 25.2% | 74.2 | 73.6 | 1.3% |
| Enroll year |  |  |  |  |  |  |
| 2011 | 941 (6.9) | 581 (6.5) | 1.7% | 6.3 | 6.3 | <0.1% |
| 2012 | 2352 (17.2) | 1697 (18.9) | 4.3% | 18.1 | 18.1 | <0.1% |
| 2013 | 2859 (20.9) | 1974 (22.0) | 2.5% | 21.4 | 21.4 | <0.1% |
| 2014 | 3288 (24.1) | 2032 (22.6) | 3.5% | 23.1 | 23.1 | <0.1% |
| 2015 | 4213 (30.9) | 2698 (30.0) | 1.8% | 31.1 | 31.1 | <0.1% |
| High tertile of income | 6563 (48.1) | 3840 (42.8) | 10.7% | 44.8 | 44.8 | <0.1% |
| Number of OPD visits ≥12/year | 11812 (86.5) | 6968 (77.6) | 23.4% | 81.7 | 81.7 | <0.1% |
| Living in metropolitan areas | 6473 (47.4) | 3778 (42.1) | 10.8% | 44.7 | 44.7 | <0.1% |
| Level of care initiating treatment |  |  |  |  |  |  |
|  Tertiary | 8570 (62.8) | 3633 (40.4) | 45.8% | 50.1 | 50.1 | <0.1% |
|  Secondary | 4661 (34.1) | 4604 (51.3) | 35.1% | 44.6 | 44.6 | <0.1% |
|  Primary | 422 (3.1) | 745 (8.3) | 22.6% | 5.3 | 5.3 | <0.1% |
| **Risk scores** |  |  |  |  |  |  |
| CHA2DS2-VASc score | 422 (3.1) | 745 (8.3) | 22.6% | 4 (3-5) | 4 (3-5) | <0.1% |
| HAS-BLED score\* | 422 (3.1) | 745 (8.3) | 22.6% | 3 (2-3) | 3 (2-3) | <0.1% |
| Charlson comorbidity index  | 422 (3.1) | 745 (8.3) | 22.6% | 4 (2-6) | 4 (2-6) | <0.1% |
| Hospital Frailty Risk score  | 2.8 (0.3-6.8) | 2.8 (0.1-7.0) | 2.4% | 3.0 (0.5-7.1) | 2.9 (0.3-7.1) | <0.1% |
| **Medical history** |  |  |  |  |  |  |
| Heart failure | 7431 (54.4) | 4933 (54.9) | 1.0% | 54.9 | 54.9 | <0.1% |
| Previous hospitalization for heart failure | 1835 (13.4) | 1368 (15.2) | 5.1% | 14.5 | 14.5 | <0.1% |
| Hypertension | 11923 (87.3) | 6094 (67.8) | 48.0% | 80.3 | 80.3 | <0.1% |
| Diabetes | 4336 (31.8) | 2310 (25.7) | 13.4% | 29.6 | 29.6 | <0.1% |
| Dyslipidemia | 11990 (87.8) | 6934 (77.2) | 28.2% | 83.4 | 83.4 | <0.1% |
| Ischemic stroke | 4423 (32.4) | 3295 (36.7) | 9.0% | 35.8 | 35.8 | <0.1% |
| Transient ischemic attack | 1643 (12.0) | 785 (8.7) | 10.8% | 10.4 | 10.4 | <0.1% |
| Hemorrhagic stroke | 387 (2.8) | 249 (2.8) | 0.4% | 2.9 | 2.9 | <0.1% |
| Myocardial infarction | 1510 (11.1) | 605 (6.7) | 15.2% | 8.6 | 8.6 | <0.1% |
| Peripheral arterial disease | 2363 (17.3) | 1076 (12.0) | 15.1% | 14.6 | 14.6 | <0.1% |
| Valvular heart disease | 1568 (11.5) | 1047 (11.7) | 0.5% | 11.5 | 11.5 | <0.1% |
| Chronic kidney disease | 1113 (8.2) | 428 (4.8) | 13.8% | 6.3 | 6.3 | <0.1% |
| Proteinuria | 1041 (7.6) | 613 (6.8) | 3.1% | 7.5 | 7.5 | <0.1% |
| Hyperthyroidism | 2074 (15.2) | 751 (8.4) | 21.3% | 10.8 | 10.8 | <0.1% |
| Hypothyroidism | 2177 (15.9) | 905 (10.1) | 17.5% | 12.4 | 12.4 | <0.1% |
| Malignancy | 3467 (25.4) | 2067 (23.0) | 5.6% | 24.7 | 24.7 | <0.1% |
| Chronic obstructive pulmonary disease | 4471 (32.7) | 2776 (30.9) | 4.0% | 32.3 | 32.3 | <0.1% |
| Chronic liver disease | 6330 (46.4) | 3388 (37.7) | 17.6% | 41.9 | 41.9 | <0.1% |
| Hypertrophic cardiomyopathy | 311 (2.3) | 94 (1.0) | 9.6% | 1.5 | 1.5 | <0.1% |
| Osteoporosis | 4930 (36.1) | 3154 (35.1) | 2.1% | 35.6 | 35.6 | <0.1% |
| Sleep apnea | 99 (0.7) | 34 (0.4) | 4.7% | 0.5 | 0.5 | <0.1% |
| **Concurrent medication** |  |  |  |  |  |  |
| Oral anticoagulant | 13653 (100.0) | 8982 (100.0) | <0.1% | 100.0 | 100.0 | <0.1% |
| Warfarin | 10950 (80.2) | 7525 (83.8) | 9.3% | 82.4 | 82.4 | <0.1% |
| Direct oral anticoagulant | 3464 (25.4) | 1955 (21.8) | 8.5% | 23.3 | 23.3 | <0.1% |
| Beta-blocker | 6524 (47.8) | 6481 (72.2) | 51.4% | 69.2 | 69.2 | <0.1% |
| Non-dihydropyridine CCB | 1759 (12.9) | 1377 (15.3) | 7.0% | 16.3 | 16.3 | <0.1% |
| Digoxin | 1106 (8.1) | 2927 (32.6) | 63.9% | 18.3 | 18.3 | <0.1% |
| Aspirin | 3015 (22.1) | 1662 (18.5) | 8.9% | 20.3 | 20.3 | <0.1% |
| P2Y12 inhibitor | 1279 (9.4) | 759 (8.5) | 3.2% | 9.3 | 9.3 | <0.1% |
| Statin | 6213 (45.5) | 3952 (44.0) | 3.0% | 46.0 | 46.0 | <0.1% |
| Dihydropyridine CCB | 2897 (21.2) | 1170 (13.0) | 21.9% | 16.4 | 16.4 | <0.1% |
| ACEI/ARB | 7329 (53.7) | 4767 (53.1) | 1.2% | 53.3 | 53.3 | <0.1% |
| Loop/thiazide diuretics | 5536 (40.5) | 4715 (52.5) | 24.1% | 46.8 | 46.8 | <0.1% |
| K+ sparing diuretics | 1970 (14.4) | 2105 (23.4) | 23.1% | 19.0 | 19.0 | <0.1% |
| Alpha-blocker | 290 (2.1) | 169 (1.9) | 1.7% | 1.9 | 1.9 | <0.1% |

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

\*A liable international normalized ratio was not assessed.

ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; ASD, absolute standardized difference; OPD, outpatient department.