**Dronedarone vs. Sotalol in Anti-Arrhythmic Drug Naïve Veterans with Atrial Fibrillation**

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**Short Title**: Dronedarone vs. Sotalol in Atrial Fibrillation

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**Manuscript Word Count**: 3274

**ABSTRACT**

**BACKGROUND**

Sotalol and dronedarone are both used for maintenance of sinus rhythm for patients with atrial fibrillation (AF). However, while sotalol requires initial monitoring for QT prolongation and pro-arrhythmia, dronedarone does not. These treatments can be used in comparable patients, but their safety and effectiveness have not been compared head-to-head. Therefore, we retrospectively evaluated the effectiveness and safety using data from a large health care system.

**METHODS**

Using Veterans Health Administration data, we identified 11,296 AAD-naïve patients with AF prescribed dronedarone or sotalol in 2012 or later. We excluded patients with prior conduction disease, pacemakers or implantable cardioverter-defibrillators, ventricular arrhythmia, cancer, renal failure, liver disease, or heart failure. We used natural language processing to identify and compare baseline left ventricular ejection fraction (LVEF) between treatment arms. We used 1:1 propensity score matching, based on patient demographics, comorbidities, and medications, and Cox regression to compare strategies. To evaluate residual confounding, we performed falsification analysis with non-plausible outcomes.

**RESULTS**

The matched cohort comprised 6,212 patients (3,106 dronedarone, 3,106 sotalol; mean(±SD) age 71±10 yrs, 2.5% female, mean(±SD) CHA2DS2-VASC 2±1.3). The mean(±SD) LVEF was 55±11 and 58±10 for dronedarone and sotalol users, correspondingly. Dronedarone, compared with sotalol, did not demonstrate a significant association with risk of cardiovascular hospitalization (hazard ratio (HR):1.03, 95% confidence interval (CI):0.88–1.21) or all-cause mortality (HR:0.89, 95% CI:0.68–1.16). However, dronedarone was associated with significantly lower risk of ventricular pro-arrhythmic events (HR:0.53, 95% CI:0.38–0.74) and symptomatic bradycardia (HR:0.56, 95% CI:0.37–0.87). The primary findings were stable across sensitivity analyses. Falsification analyses were not significant.

**CONCLUSION**

Dronedarone, compared with sotalol, was associated with a lower risk of ventricular pro-arrhythmic events and conduction disorders while having no difference in risk of incident cardiovascular hospitalization and mortality. These observational data provide the basis for prospective efficacy and safety trials.

**CLINICAL PERSPECTIVES**

**What is new?**

* Among anti-arrhythmic drug naïve veterans with atrial fibrillation, rhythm control with dronedarone vs sotalol was not significantly different for the outcomes of cardiovascular hospitalization and death.
* Dronedarone, compared with sotalol, was associated with lower rates of ventricular pro-arrhythmia events and conduction disorders.

**What are the clinical implications?**

* Dronedarone’s safety profile may make it preferable as a first-line anti-arrhythmic drug for rhythm control in atrial fibrillation patients without severe systolic dysfunction or unstable heart failure.
* Prospective clinical trials are needed to validate these comparative safety findings.
* Medication discontinuation rates were high with both dronedarone and sotalol, and may represent an area of focus for targeted interventions.

**ABBREVIATIONS**

AAD: Anti-arrhythmic drug

AF: Atrial fibrillation

ICD: International Classification of Diseases

VA: Veterans Health Administration

**INTRODUCTION**

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting more than 6 million American adults and more than 44 million individuals worldwide.1,2 The primary goals of AF therapy include (1) preventing ischemic stroke with oral anticoagulation, (2) reducing the risk of heart failure or hospitalization as a result of AF, and (3) improving quality of life.3 While early studies suggested that rate and rhythm control approaches were equivalent,4 contemporary studies with modern anti-arrhythmic drugs (AADs) and less concomitant digoxin use5 have indicated that rhythm control is associated with lower rates of cardiovascular events and hospitalization.6,7

In patients with AF and heart failure, catheter ablation appears to significantly reduce AF burden and frequency of AF recurrence compared to pharmacologic rhythm control.8 For AF patients without heart failure, current professional society guidelines offer a variety of AAD options, including amiodarone, dofetilide, dronedarone, flecainide, propafenone, and sotalol.2,3 Of these options, dofetilide, dronedarone and sotalol are recommended as initial options for patients with existing structural heart disease or coronary artery disease, although dofetilide is not available in Europe or Australia.

While dronedarone and sotalol both have Vaughan Williams class II and class III AAD properties, there are limited observational studies and no randomized controlled trials comparing these drugs head-to-head. We therefore used national data from the United States Veterans Affairs Health Administration to compare effectiveness and safety outcomes between dronedarone and sotalol in AAD-naïve patients with AF.

**METHODS**

We performed a retrospective cohort study using data from the United States Veterans Health Administration (VA), the largest integrated healthcare system in the United States. The study database was created by combining medical claims and electronic health records from the VA National Patient Care Database,9 the VA Decision Support System national pharmacy extract,10 the VA Fee Basis Inpatient and Outpatient datasets, the VA Laboratory Decision Support System extract,11 Medicare inpatient and outpatient claims data (part A, part B, and carrier files),12 and the VA Vital Status file, which provided validated mortality data by combining Medicare, VA and Social Security Administration data.13,14 Methods for data linkage have been previously detailed.5,15,16

This study was approved by the local institutional review board (Stanford, CA) and the VA Research and Development Committee (Palo Alto, CA). Data are not available to share because of data use agreements and restrictions on use of Veteran data, but access to the master files may be requested from the VA Informatics and Computing Infrastructure by eligible investigators.

Study Cohort

We included patients who were first prescribed dronedarone or sotalol on or after January 1, 2012 with at least one ambulatory or inpatient diagnosis of AF within the previous 180 days. The date of dronedarone or sotalol prescription was the index date. We excluded patients who had (1) less than 180 days of continuous healthcare system enrollment prior to the index date, (2) less than 6 months of follow-up available after the index date, (3) any prior use of an AAD (amiodarone, disopyramide, dronedarone, dofetilide, flecainide, propafenone or sotalol), (4) cancer diagnosis, (5) end-stage renal disease, kidney transplant, or severe hepatic impairment, (6) prior hospitalization for heart failure, (7) pacemaker or implantable cardioverter-defibrillator, (8) prior 2nd or 3rd degree atrioventricular block or ventricular pro-arrhythmia, or (9) were < 18 years of age or had missing age (pertinent international classification of disease [ICD] codes are listed in **Supplemental Table 1**). We also excluded patients on a combined total daily sotalol dose < 160 mg on the index date, the lowest FDA labeled dose for management of AF in patients without chronic kidney disease.17 **Figure 1** summarizes the study design and assessment windows for inclusion, exclusions, and covariates.

Baseline characteristics and covariates were identified using previously described and validated methods using the cross-linked dataset detailed above.5,18,19 In the VA, left ventricular ejection fraction (LVEF) has been extracted from 2012 onward using natural language processing of echocardiography reports, radiologic reports, and clinical notes, with a positive predictive value exceeding 95%.20,21 LVEF was ascertained within the 180 days prior to the index date, excluding extreme/non-plausible values (<10% or >75%). For patients with more than one LVEF, we used the chronologically most recent value.

Exposures

The primary exposures were sotalol or dronedarone. Patients were deemed to have continuous exposure as long as there were no gaps >30 days in prescription coverage, based on pill counts and subsequent prescription fills. Patients were censored if they had gaps >30 days or if the prescription was discontinued.

Propensity Score Matching

To compare the safety and clinical outcomes of dronedarone and sotalol, we performed propensity score matching (PSM) to balance baseline covariates and identify parallel treatment cohorts. Propensity scores were calculated using logistic regression, with conditional probability of dronedarone prescription. A matching caliper of 0.03 was used to match patients using greedy nearest neighbor matching with a 1:1 ratio. The primary covariates included demographic factors, AF diagnosis history, healthcare utilization, comorbidities, and concomitant medications, as noted in **Table 1**. Baseline LVEF was not used for propensity matching as it was only available in 51% of patients. Balance diagnostics were assessed using standardized difference in baseline covariates before and after PSM and visual examination of the overlap in distribution of propensity scores. A standardized difference after PSM <0.1 is generally deemed acceptable (**Table 1**).22

Outcomes

For our study outcomes, we deconstructed the primary cardiovascular hospitalization outcome from the ATHENA trial7 and incorporated pro-arrhythmia definitions from the EURIDIS/ADONIS and DIONYSOS trials.23,24 The primary outcomes were (1) cardiovascular hospitalization, defined as an inpatient claim with an ICD code for myocardial infarction, stroke, transient ischemic attack, heart failure, or AF in the primary diagnosis position; and (2) ventricular pro-arrhythmia, defined as an ambulatory or inpatient claim with an ICD code for ventricular fibrillation/flutter, ventricular tachycardia, torsades de pointes, re-entry ventricular arrhythmia, or cardiac arrest in any diagnosis position. Secondary outcomes included (1) all-cause mortality, (2) conduction disorders, (3) symptomatic bradycardia, and (4) bradycardia with pacemaker insertion. The ICD codes for all outcomes are listed in **Supplemental Table 2.**

Falsification

To quantify residual confounding in the cohorts, we performed a falsification analysis using a composite outcome that could not be reasonably associated with either treatment arm or cardiovascular disease. This approach has been previously described in observational comparisons of AADs.25,26 The primary falsification endpoint was the composite incidence of hip fractures, cancer, and infections (pertinent ICD codes listed in **Supplemental Table 2**).

**Statistical Analysis**

Baseline characteristics were stratified by patient treatment arm. Incidence rates of each primary and secondary outcome were identified and reported per 100 patient-years. To evaluate the association of treatment group with the outcomes of interest, we used a Cox proportional hazards model among the matched cohort. Each outcome was evaluated independently, and patients were censored upon (1) occurrence of outcome, (2) death, (3) index treatment discontinuation, (4) use of other class I or class III AAD, or (5) end of follow-up. We ensured there were no violations of the proportional hazards assumption by (1) visually evaluating the Schoenfeld residuals, (2) performing the global test of proportional hazards, and (3) plotting Kaplan-Meier curves for the primary and secondary outcomes.

To evaluate the potential for unmeasured confounding, we also calculated E-values.27 The E-value represents the strength of association an unmeasured confounder would need to have with both exposure (i.e., sotalol) and outcome to account for the observed results.

All analyses were performed with SAS version 9.4 (Cary, NC) and STATA version 16.0 (College Station, TX). The senior author had full access to all study data and takes responsibility for its integrity and the data analysis.

Sensitivity Analyses

We performed a series of sensitivity analyses to test the consistency of the associations from the primary analyses. First, to account for unequal medication adherence or persistence between the groups, we performed an intention-to-treat analysis in which patients were not censored at the time of medication discontinuation. Second, since QT prolongation is a potential adverse effect of class III AADs, we performed a sensitivity analysis in which the outcome of ventricular pro-arrhythmia also included QT prolongation (ICD-9 code 426.82, ICD-10 code I45.81). Third, since a fixed time period for covariate acquisition may lead to underestimation of baseline comorbidities, we performed a sensitivity analysis in which covariates were assessed based on all available data prior to the index date. Fourth, since the primary recommended treatment approach for atrial flutter is catheter ablation and not AADs,3 we performed a sensitivity analysis in which patients with atrial flutter were excluded from the analysis cohort. Fifth, while the FDA recommends sotalol be initiated in a facility that can provide cardiac resuscitation and electrocardiographic monitoring, inpatient administration of medications is not well captured in claims databases. Therefore, to address potential time zero selection bias in patients who would have had to survive to outpatient prescription fills, we performed a sensitivity analysis for the primary outcomes in which patients with a hospitalization for AF within one week of the index date were excluded from the analysis cohort. Sixth, to address the potential for imbalance in the LVEF between cohorts to affect clinical outcomes, we added an additional sensitivity analysis in which we introduced a categorical variable for LVEF with the following labels: (1) LVEF ≥ 50%, (2) LVEF 41-49%, (3) LVEF ≤ 40%, (4) LVEF missing with history of systolic heart failure, and (5) LVEF missing with no history of systolic heart failure. We then repeated the PSM and the Cox proportional hazard regressions for the primary outcomes. Finally, since propensity matching prior has the potential to influence standard error estimates by creating clustering between matched pairs, we performed a sensitivity analysis in which we repeated the Cox proportional hazard regressions for the primary and secondary outcomes using cluster-robust standard errors with clustering by matched pairs.

**RESULTS**

The initial cohort, after inclusion and exclusion criteria were applied, included 11,296 patients (**Figure 2**). After PSM, the analysis cohort comprised 6,212 patients (mean [±SD] age 71±10 years; 97.6% male; 92% white; mean [±SD] CHA2DS2-VASc score 2±1.3; 3106 patients on dronedarone and 3106 patients on sotalol; **Table 1**). There was a high burden of baseline comorbid illness, including hypertension (sotalol: 65.2%, dronedarone: 64.3%), ischemic heart disease (sotalol: 41.1%, dronedarone: 40.9%), heart failure (sotalol: 9.6%, dronedarone: 10.0%), and diabetes (sotalol: 28.6%, dronedarone: 28.4%). At the index date, 53.9% of sotalol users and 53.3% of dronedarone users were on oral anticoagulation, respectively. The cohorts were well-balanced with standardized mean differences < 0.1 (**Table 1**) and alignment of the propensity score disributions after PSM (**Supplemental Figure 1**).

Demographic and clinical characteristics not used in the PSM are reported in **Supplemental Table 3**. The baseline LVEF within 180 days prior to the index date was available for 1,771 sotalol users and 1,401 dronedarone users, and was 55±11 and 58±10, correspondingly (standardized mean difference 0.216).

Primary outcomes

The first primary outcome of cardiovascular hospitalization occurred in 310 (10%) patients on dronedarone and 296 (9.5%) patients on sotalol. The 24 month incidence of cardiovascular hospitalization was similar between dronedarone and sotalol at 10.2 (95% confidence interval [CI]: 9.0-11.6) and 10.7 [95% CI: 9.5-12.0] per 100 patient-years, correspondingly (**Table 2**). The risk of cardiovascular hospitalization was not significantly different between dronedarone and sotalol (hazard ratio [HR] 1.03, 95% CI: 0.88-1.21, p=0.729) (**Figure 3**).

The second primary outcome of ventricular pro-arrhythmia occurred in 58 (1.9%) patients on dronedarone and 91 (2.9%) patients on sotalol. Dronedarone, compared to sotalol, had a lower 24 month incidence of ventricular pro-arrhythmia: 1.8 (95% CI: 1.3-2.4) vs. 3.4 (95% CI: 2.7-4.2) per 100 patient-years, correspondingly (**Table 2**). The risk of ventricular pro-arrhythmia was significantly lower with dronedarone compared to sotalol (HR 0.53, 95% CI: 0.38-0.74, p=0.0002) (**Figure 3**). The E-value for ventricular pro-arrhythmia was 2.04 for the upper bounds of the confidence interval to be 1, and 3.18 for the point estimate to be 1.

Secondary outcomes

The 24 month incidence of all-cause mortality was similar between dronedarone and sotalol at 3.0 (95% CI: 2.4- 3.8) and 3.4 (95% CI: 2.8- 4.2) per 100 patient-years, correspondingly (**Table 3**). The risk of death was not significantly different between dronedarone and sotalol (HR: 0.89, 95% CI: 0.68-1.16, p=0.399) (**Figure 3**).

The 24 month incidence rates, per 100 patient-years, of the conduction disease secondary outcomes were as follows: conduction disorders – 16.0 (95% CI: 14.5-17.8) for dronedarone and 15.3 (95% CI: 13.8-16.9) for sotalol; symptomatic bradycardia – 0.9 (95% CI: 0.6-1.4) for dronedarone and 1.7 (95% CI: 1.2-2.2) for sotalol; bradycardia with pacemaker – 0.8 (95% CI: 0.5-1.2) for dronedarone and 1.5 (95% CI: 1.1-2.0) for sotalol (**Table 3**). Dronedarone, compared to sotalol, was associated with a lower risk of bradycardia with pacemaker (HR 0.56, 95% CI: 0.36-0.89, p=0.012) and symptomatic bradycardia (HR 0.56, 95% CI: 0.37-0.87, p=0.008) (**Figure 3**).

Falsification and sensitivity analyses

In the falsification analysis, we found no significant association between either exposure group and the falsification endpoint, with a HR of 0.89 (95% CI: 0.78-1.03).

We performed a series of sensitivity analyses, with the resultant hazard ratios for each outcome reported in **Table 4**. Overall, dronedarone continued to be associated with a lower risk of ventricular pro-arrhythmia across all sensitivity analyses. There was no significant difference in cardiovascular hospitalization or mortality across sensitivity analyses. For the secondary outcomes of bradycardia with pacemaker and symptomatic bradycardia, there was no longer a significant decrease with dronedarone therapy in the sensitivity analyses. For the sensitivity analysis including the categorical LVEF variable in the PSM, the baseline demographics and clinical characteristics were well balanced after matching (**Supplemental Table 5**). In this analysis, the risk of cardiovascular hospitalization was not significantly different between dronedarone and sotalol, but the risk of ventricular pro-arrhythmia was significantly lower with dronedarone compared to sotalol (HR 0.50, 95% CI: 0.36 – 0.69, p < 0.0001). Finally, repeating the Cox proportional hazard regressions using cluster-robust standard errors did not result in any meaningful differences in HRs, CIs, or p-values.

**DISCUSSION**

In this large retrospective cohort study of propensity-matched AAD naïve veterans with AF, we found that patients using dronedarone, compared with sotalol, had a similar risk of cardiovascular hospitalization, but lower risk of ventricular pro-arrhythmia. Dronedarone use was also associated with a lower risk of bradycardia leading to pacemaker insertion and symptomatic bradycardia. The observed association of dronedarone with lower risk of ventricular pro-arrhythmia was consistent across sensitivity analyses. The quantitative bias analysis revealed that only a strong unknown confounder associated with both sotalol use and ventricular pro-arrhythmia could account for this observation, which would be highly unlikely. Additionally, we did not find a significant association between sotalol and our falsification outcome, reducing the likelihood that the observed associations were due to residual confounding.

The clinical management of AF has continuously evolved. Initially, RACE and AFFIRM showed no significant difference in clinical outcomes between rate and rhythm control strategies in AF.28,29 However, AATAC and sub-analyses of AFFIRM then showed a net clinical benefit to more time in sinus rhythm.30,31 Other landmark studies including ATHENA and EAST-AFNET4 have since demonstrated that rhythm control is associated with lower rates of cardiovascular hospitalization and major adverse cardiovascular events with current generation AADs, continuous use of anticoagulation, and reduced concomitant digoxin use.6,7 The culmination of these studies has led to a paradigm shift with a greater focus on early rhythm control, particularly in symptomatic patients or those with heart failure.32

In a previous study of veterans with newly diagnosed AF, use of class IC AADs was associated with lower risk of cardiovascular events than dofetilide or sotalol.25 However, given the high prevalence of coronary artery disease or structural heart disease in patients with newly diagnosed AF,16,33 class IC agents are frequently not a viable option. Of the remaining AADs, amiodarone has known concerns for hepatic, pulmonary, and thyrotoxicity while dofetilide can be limited by renal insufficiency and drug-drug interactions which may lead to QT prolongation. Between dronedarone and sotalol, our findings suggest that dronedarone may be preferable given a similar effectiveness for cardiovascular hospitalization and death, but lower rates of ventricular pro-arrhythmia and conduction disease.

In our study, we observed a lower risk of ventricular pro-arrhythmia and conduction disease with dronedarone than with sotalol. While dronedarone and sotalol both have class II and class III AAD properties, previous observations on the pro-arrhythmic effects of sotalol led to an FDA recommendation that patients have at least three days of monitoring in a facility that can provide cardiac resuscitation, ECG monitoring, and calculation of creatinine clearance upon initiation of sotalol.17 Dronedarone, similar to amiodarone, also has class IV AAD properties, which may explain the low arrhythmogenicity with regards to ventricular pro-arrhythmia observed in the dronedarone clinical trials.34–36 This may also explain why sotalol continues to have a higher risk of class III adverse events than dronedarone in this study, despite selecting for patients who did not have ventricular arrhythmias or excess QT prolongation on initiation. Since the sotalol cohort only included those individuals who tolerated inpatient sotalol loading and received a subsequent outpatient prescription, our results may underestimate the true ventricular pro-arrhythmia risk associated with sotalol.

Another possible explanation for the difference in risk of ventricular pro-arrhythmia and conduction disease is confounding due to unmeasured differences in the two treatment groups. However, our initial cohorts were well matched even prior to PSM, likely owing to the similar pharmacologic properties of sotalol and dronedarone with similar indications and contraindications for the two drugs in current AF guidelines.2,3 In our falsification analysis, we found no significant differences in the risk of hip fractures, cancer, or infections between the groups. The finding of no difference in all-cause mortality between sotalol and dronedarone serves as an additional evaluation for confounding, as prior rhythm control and ablation studies in AF have not demonstrated mortality benefits.6,37 However, a trend for mortality benefit with dronedarone is reassuring, as ventricular pro-arrhythmia events with sotalol have previously been associated with increased risk for mortality. Additionally, the calculated E-values for ventricular pro-arrhythmia of 2.04 and 3.18 indicate that only a strong confounder associated with both sotalol use and ventricular pro-arrhythmia could account for the observed association. Our results were also consistent across sensitivity analyses that varied our assumptions regarding the cohort, the exposure, and the outcome. Overall, these analyses suggest unmeasured confounding is unlikely account for the observed differences between treatment groups.

Our study also found high rates of medication discontinuation in both treatment arms, accounting for approximately 70% of censoring events by 24 months. The rates of discontinuation were generally similar: 50.4% for dronedarone vs. 53.1% for sotalol at 6 months, and 59.6% for dronedarone vs 55.8% for sotalol at 12 months. We are not able to retrospectively ascertain the reasons for discontinuation, which may include lack of effectiveness, drug-related adverse events, patient intolerance, lapses in prescription or unfilled prescriptions, intended short-term use (either after cardioversion, ablation, or inciting event), or provider preference. While the relative contributions of each of these may differ between treatment groups, our results were consistent with an intention-to-treat analysis that did not censor for drug discontinuation. Further studies on differences in AAD persistence and adherence may provide insights on patient-specific factors that favor use of one treatment over the other. With increasing momentum toward early rhythm control in AF, understanding these differences and developing targeted provider- and systems-level interventions may be a means to improving AF-related outcomes.

Limitations

Our study has important limitations, most notably that the study design is retrospective with limited sample size and rationale for treatment selection cannot be ascertained, so residual confounding by indication is a possibility. Patient frailty is a potential example of such a confounder. While we did not observe a statistically significant associations with the falsification endpoint, the point estimate below 1 introduces the possibility that confounding may have contributed to our findings. Second, this is a veteran’s cohort that is predominantly male, which may limit the generalizability of the findings to non-veterans, and underestimate the risk of pro-arrhythmia in women, who have a higher risk of torsades de pointes than men.38 Third, due to the lack of reliability of ICD codes in separating paroxysmal from non-paroxysmal AF, we could not match patients based on individual AF burden or severity, or infer treatment effects by AF subtype. Fourth, we used cardiovascular hospitalization as a proxy marker for effectiveness of rhythm control of dronedarone and sotalol per prior FDA guidance and landmark clinical trials. However, this does not directly evaluate recurrence or progression of AF over time, which is beyond the scope of our work. Fifth, while we performed propensity score matching for OAC use at the time of AAD initiation, there were residual imbalances in the rates of apixaban and warfarin use with absolute standardized mean differences of 0.109 and 0.123, correspondingly. The imbalance may have had an effect on rates of cardiovascular hospitalization or mortality, although we expect the effect to be small given the imbalance is small. Also, outcome ascertainment of ventricular pro-arrhythmia based on ICD codes is not well validated and may over- or underestimate the true number of events. However, we would expect this to be similar across study arms and not meaningfully impact our results. We do not report the incidence rates for the individual components of the ventricular pro-arrhythmia endpoint as this would convey an unwarranted level of certainty as to the specific type of ventricular pro-arrhythmic event. This could lead readers to interpret associations for which our study is not designed.

Conclusions

In this large retrospective study of propensity-matched AAD-naïve patients with AF, dronedarone, compared to sotalol, was associated with lower risk of ventricular pro-arrhythmia and conduction disorders. The findings were consistent across sensitivity analyses with an intention-to-treat approach, inclusion of QT prolongation within the definition of ventricular pro-arrhythmia, using a baseline covariate assessment without time limitation, excluding atrial flutter, and excluding patients with recent hospitalization for AF. The non-significant results in the falsification analysis and high E-value reduce the likelihood that residual confounding explains the differences across treatment arms. Prospective clinical trials are needed to corroborate these findings.

**ACKNOWLEDGEMENTS**

We thank Charlotte Singh, Sanofi for providing additional critical review.

**SOURCES OF FUNDING**

This manuscript is the result of work supported with resources and the use of facilities at the VA Palo Alto Health Care System. The study was sponsored by Sanofi.

**DISCLOSURES**

**K. Pundi:** Research grants from the American Heart Association and the American College of Cardiology. Consultant for Evidently and 100Plus.

**J. Fan:** None.

**S. Kabadi**: Employee and shareholder at Sanofi.

**N. Din:** None.

**C. Blomstrom-Lundqvist:** Personal fees from Bayer, Medtronic, CathPrint, Octopus, Sanofi Aventis, Boston Sci, Merck Sharp & Dohme, Abbotts and Philips

**A. John Camm**: Personal fees from Bayer, Daiichi Sankyo, Pfizer/BMS, Medtronic Abbott, Boston Scientific, Menarini and Sanofi.

**P. Kowey:** Ad hoc consultant for Sanofi.

**J. Singh**: Consultant for Abbott, Biotronik, Boston Sci, Cardiologs, Medtronic, Implicity, Cardiac Rhythm Group, Sanofi, EBR, Microport, Biosense Webster, Sanofi & Orchestra BioMed.

**J. Rashkin**: Employee at Sanofi.

**M. Wieloch**: Employee and shareholder at Sanofi.

**M. Turakhia:** Research grants from Bristol Myers Squibb, American Heart Association, Apple Inc, Bayer, and the Food and Drug Administration. Consultant for Medtronic, Abbott, Biotronik, Sanofi, Pfizer, Myokardia, Johnson & Johnson, Milestone, InCarda, 100Plus, Alivecor, Acutus Medical, and BrightInsight.

**A. Sandhu:** Research grant 1K23HL151672-01 from the National Heart, Lung, and Blood Institute.

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**FIGURES WITH FIGURE LEGENDS**



**Figure 1. Study Design**. The primary analytic cohort consisted of patients prescribed dronedarone or sotalol (at least 160 mg daily combined dose), with the above noted inclusion and exclusion criteria. The index date was the date of dronedarone or sotalol prescription. Covariates for propensity matching were assessed in the 180 days prior to the index date. Patients were followed from the index date until occurrence of outcome, death, medication discontinuation, use of other anti-arrhythmic, or end of follow-up.



**Figure 2. Cohort selection diagram**. Inclusion and exclusion criteria used to select initial analysis cohort.



**Figure 3. Association of treatment group with primary and secondary outcomes**. Hazard ratios for each of the primary and secondary outcomes in the primary analysis using Cox proportional hazard regression. Error bars represents 95% confidence intervals. \*CI: Confidence Interval.

**TABLES**

**Table 1.** Baseline demographics and clinical characteristics before and after propensity matching.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variable** | **Prior to Matching** | | **Standardized Mean Difference** | **Matched Cohort** | | **Standardized Mean Difference\*** |
| **Sotalol** | **Dronedarone** | **Sotalol** | **Dronedarone** |
| **Number of patients** | 8,190 | 3,106 |  | 3,106 | 3,106 |  |
| **Cohort Entry Year** |  | | |  | | |
| ...2012; n (%) | 836 (10.2%) | 229 (7.4%) | 0.157 | 259 (8.3%) | 229 (7.4%) | 0.075 |
| ...2013; n (%) | 779 (9.5%) | 241 (7.8%) | 240 (7.7%) | 241 (7.8%) |
| ...2014; n (%) | 841 (10.3%) | 273 (8.8%) | 288 (9.3%) | 273 (8.8%) |
| ...2015; n (%) | 886 (10.8%) | 347 (11.2%) | 343 (11.0%) | 347 (11.2%) |
| ...2016; n (%) | 979 (12.0%) | 425 (13.7%) | 413 (13.3%) | 425 (13.7%) |
| ...2017; n (%) | 1,022 (12.5%) | 379 (12.2%) | 365 (11.8%) | 379 (12.2%) |
| ...2018; n (%) | 1,021 (12.5%) | 415 (13.4%) | 410 (13.2%) | 415 (13.4%) |
| ...2019; n (%) | 1,034 (12.6%) | 448 (14.4%) | 434 (14.0%) | 448 (14.4%) |
| ...2020; n (%) | 792 (9.7%) | 349 (11.2%) | 354 (11.4%) | 349 (11.2%) |
| ...2021; n (%) |  |  |  |  |  |  |
| **Age categories (in years)** |  | | |  | | |
| ...18 - 34; n (%) | 22 (0.27%) | 12 (0.39%) | 0.298 | 10 (0.32%) | 12 (0.39%) | 0.037 |
| ...35 - 44; n (%) | 66 (0.81%) | 33 (1.1%) | 35 (1.1%) | 33 (1.1%) |
| ...45 - 54; n (%) | 412 (5.0%) | 148 (4.8%) | 141 (4.5%) | 148 (4.8%) |
| ...55 - 64; n (%) | 1,776 (21.7%) | 479 (15.4%) | 481 (15.5%) | 479 (15.4%) |
| ...65 - 74; n (%) | 3,951 (48.3%) | 1,380 (44.4%) | 1,374 (44.2%) | 1,380 (44.4%) |
| ...75 - 84; n (%) | 1,570 (19.2%) | 760 (24.5%) | 761 (24.5%) | 760 (24.5%) |
| ...>= 85; n (%) | 393 (4.8%) | 294 (9.5%) | 304 (9.8%) | 294 (9.5%) |
| **Gender categories** |  | | |  | | |
| ...Male; n (%) | 8,012 (97.8%) | 3,030 (97.5%) | 0.018 | 3,031 (97.6%) | 3,030 (97.6%) | 0.002 |
| ...Female; n (%) | 178 (2.2%) | 76 (2.5%) | 75 (2.4%) | 76 (2.5%) |
| ...Missing or Unknown; n (%) | 0 | 0 | 0 | 0 |
| **Race/ethnicity** |  | | |  | | |
| ...White; n (%) | 7459 (91.4%) | 2,857 (92.0%) | 0.064 | 2,852 (91.8%) | 2,857 (92.0%) | 0.076 |
| ...African American; n (%) | 490 (6.0%) | 176 (5.7%) | 166 (5.3%) | 176 (5.7%) |
| ...Hispanic; n (%) | 12 (0.15%) | 3 (0.10%) | 6 (0.19%) | 3 (0.10%) |
| ...Other/Unknown/Missing; n (%) | 229 (2.8%) | 70 (2.3%) | 82 (2.6%) | 70 (2.3%) |
| **Region - US** |  | | |  | | |
| ...Northeast; n (%) | 1,357 (16.6%) | 447 (14.4%) | 0.140 | 431 (13.9%) | 447 (14.4%) | 0.032 |
| ...Midwest; n (%) | 2,675 (32.7%) | 1,001 (32.2%) | 1,010 (32.5%) | 1,001 (32.2%) |
| ...Southeast; n (%) | 3,281 (40.1%) | 1,246 (40.1%) | 1,249 (40.2%) | 1246 (40.1%) |
| ...West; n (%) | 876 (10.7%) | 408 (13.1%) | 413 (13.3%) | 408 (13.1%) |
| ...Other/Unknown; n (%) | 1 (0.01%) | 4 (0.13%) | 3 (0.10%) | 4 (0.13%) |
| **Type of AF#** |  | | |  | | |
| ...Unknown AF (ICD-9 only); n (%) | 3,145 (38.4%) | 1,017 (32.7%) | 0.260 | 1,065 (34.3%) | 1,017 (32.7%) | 0.035 |
| ...Unspecified AF; n (%) | 1,837 (22.4%) | 605 (19.5%) | 567 (18.3%) | 605 (19.5%) |
| ...Paroxysmal AF; n (%) | 1,593 (19.5%) | 947 (30.5%) | 942 (30.3%) | 947 (30.5%) |
| ...Persistent AF; n (%) | 643 (7.9%) | 204 (6.6%) | 209 (6.7%) | 204 (6.6%) |
| ...Permanent AF; n (%) | 972 (11.9%) | 333 (10.7%) | 323 (10.4%) | 333 (10.7%) |
| **Setting of first AF diagnosis** |  | | |  | | |
| ...Inpatient; n (%) | 1,150 (14.0%) | 268 (8.6%) | 0.158 | 255 (8.2%) | 268 (8.6%) | 0.055 |
| ...ER; n (%) | 439 (5.4%) | 166 (5.3%) |  | 174 (5.6%) | 166 (5.3%) |  |
| ...Outpatient; n (%) | 6,601 (80.6%) | 2,672 (86.0%) |  | 2,677 (86.2%) | 2,672 (86.0%) |  |
| **Months between first diagnosis of AF and index date** |  | | | | | |
| ...mean (STD) | 2.22 (2.11) | 2.24 (1.97) | 0.008 | 2.28 (2.09) | 2.24 (1.97) | 0.020 |
| ...median [IQR] | 2.00 [0.00, 4.00] | 2.00 [1.00, 4.00] |  | 2.00 [0.00, 4.00] | 2.00 [1.00, 4.00] |  |
| **Medical History** |  | | | | | |
| History of ablation; n (%) | 30 (0.4%) | 15 (0.5%) | 0.018 | 15 (0.48%) | 15 (0.48%) | 0.000 |
| Cardiomyopathy or congenital anomalies of the heart; n (%) | 688 (8.4%) | 192 (6.2%) | 0.085 | 184 (5.9%) | 192 (6.2%) | 0.011 |
| Chronic kidney disease; n (%) | 442 (5.4%) | 274 (8.8%) | 0.134 | 260 (8.4%) | 274 (8.8%) | 0.016 |
| Heart failure; n (%) | 1,341 (16.4%) | 311 (10.0%) | 0.189 | 297 (9.6%) | 311 (10.0%) | 0.015 |
| Diabetes Mellitus; n (%) | 2,873(35.1%) | 881 (28.4%) | 0.145 | 889 (28.6%) | 881 (28.4%) | 0.006 |
| Hypertension; n (%) | 5,637 (68.8%) | 1,997 (64.3%) | 0.096 | 2,026 (65.2%) | 1,997 (64.3%) | 0.011 |
| Coronary artery disease; n (%) | 3,416 (41.7%) | 1,270 (40.9%) | 0.017 | 1,277 (41.1%) | 1,270 (40.9%) | 0.005 |
| Myocardial infarction; n (%) | 220 (2.7%) | 41 (1.3%) | 0.098 | 35 (1.1%) | 41 (1.3%) | 0.018 |
| Peripheral artery disease; n (%) | 386 (4.7%) | 143 (4.6%) | 0.005 | 140 (4.5%) | 143 (4.6%) | 0.005 |
| Stroke or TIA; n (%) | 274 (3.4%) | 89 (2.9%) | 0.028 | 99 (3.2%) | 89 (2.9%) | 0.019 |
| **Number of non-AF hospitalizations** |  | | | | | |
| ...mean (STD) | 0.55 (0.90) | 0.28 (0.69) | 0.330 | 0.28 (0.69) | 0.28 (0.69) | 0.001 |
| ...median [IQR] | 0.00 [0.00, 1.00] | 0.00 [0.00, 0.00] |  | 0.00 [0.00, 0.00] | 0.00 [0.00, 0.00] |  |
| **Time since last cardioversion** |  | | | | | |
| ...No previous cardioversion; n (%) | 7,296 (89.1%) | 2,943 (94.8%) | 0.209 | 2,962 (95.4%) | 2,943 (94.8%) | 0.028 |
| ...Cardioversion within previous 2 days; n (%) | 328 (4.0%) | 32 (1.0%) | 35 (1.0%) | 32 (1.0%) |
| ...Cardioversion more than 2 days before; n (%) | 652 (8.0%) | 138 (4.4%) | 116 (3.7%) | 138 (4.4%) |
| **Medications** |  | | | | | |
| Anticoagulants; n (%) | 4,178 (51.0%) | 1,654 (53.3%) | 0.045 | 1,673 (53.9%) | 1,654 (53.3%) | 0.012 |
| Apixaban; n (%) | 1,315 (16.1%) | 742 (23.9%) | **0.197** | 602 (19.4%) | 742 (23.9%) | **0.109** |
| Dabigatran; n (%) | 717 (8.8%) | 227 (7.3%) | 0.053 | 258 (8.3%) | 227 (7.3%) | 0.037 |
| Edoxaban; n (%) | 17 (0.21%) | 6 (0.19%) | 0.003 | 11 (0.35%) | 6 (0.19%) | 0.031 |
| Rivaroxaban; n (%) | 723 (8.8%) | 342 (11.0%) | 0.073 | 314 (10.1%) | 342 (11.0%) | 0.029 |
| Warfarin; n (%) | 1,611 (19.7%) | 421 (13.6%) | **0.165** | 560 (18.0%) | 421 (13.6%) | **0.123** |
|  |  |  |  |  |  |  |
| Digoxin; n (%) | 465 (5.7%) | 132 (4.3%) | 0.066 | 148 (4.8%) | 132 (4.3%) | 0.025 |
| Beta-blockers; n (%) | 3,897 (47.6%) | 1,531 (49.3%) | 0.034 | 1,506 (48.5%) | 1,531 (49.3%) | 0.016 |
| Calcium-channel blockers; n (%) | 2,354 (28.7%) | 862 (27.8%) | 0.022 | 875 (28.2%) | 862 (27.8%) | 0.009 |
| Ezetimibe; n (%) | 72 (0.9%) | 21 (0.7%) | 0.023 | 25 (0.8%) | 21 (0.7%) | 0.015 |
| Statins; n (%) | 4,673 (57.1%) | 1,711 (55.1%) | 0.04 | 1,721 (55.4%) | 1,711 (55.1%) | 0.006 |
| PCSK9 inhibitor; n (%) | 5 (0.06%) | 1 (0.03%) | 0.001 | 1 (0.03%) | 1 (0.03%) | 0 |
| Pulmonary medications**†**; n (%) | 1,733 (21.2%) | 686 (22.1%) | 0.023 | 703 (22.6%) | 686 (22.1%) | 0.013 |
| **AF: Atrial fibrillation; IQR: Interquartile range; STD: Standard deviation**  **\*An absolute standardized mean difference <0.1 after propensity score matching is generally deemed acceptable.**  **#Based on most recent atrial fibrillation diagnosis code in the 180 days prior to index prescription date. Patients with ICD codes for permanent AF were not excluded from analysis due to poor specificity of codes to actual AF burden.**  **†Any outpatient prescription in the ascertainment period with a World Health Organization Anatomical Therapeutic Chemical Classification prefix of “R03”** | | | | | | |

**Table 2.** Incidence rates of primary outcomes, by exposure group.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  |  |  |  |
|  | **Cardiovascular hospitalization** | | **Ventricular pro-arrhythmia** | |
|  | **Dronedarone** | **Sotalol** | **Dronedarone** | **Sotalol** |
| **Follow-Up** |  |  |  |  |
| Patient years, total | 3307 | 3035 | 3549 | 3146 |
| Median [IQR] per patient | 0.5 (0.2-1.2) | 0.5 (0.2-1.3) | 0.5 (0.2-1.3) | 0.5 (0.2-1.3) |
|  |  |  |  |  |
| **Reasons for Censoring by 24 months** |  |  |  |  |
| Occurrence of outcome; n (%) | 250 (8.0%) | 270 (8.7%) | 44 (1.4%) | 91 (2.9%) |
| End of data; n (%) | 451 (14.5%) | 455 (14.7%) | 480 (15.5%) | 475 (15.3%) |
| Death; n (%) | 68 (2.2%) | 74 (2.4%) | 71 (2.3%) | 83 (2.7%) |
| Medication discontinuation; n (%) | 2225 (71.6%) | 2199 (70.8%) | 2356 (75.9%) | 2310 (74.4%) |
| Switched to other AAD; n (%) | 112 (3.6%) | 108 (3.5%) | 155 (5.0%) | 147 (4.7%) |
|  |  |  |  |  |
| **Outcome Incidence (per 100 patient-years)** |  |  |  |  |
| Total; n (%) | 310 (10.0%) | 296 (9.5%) | 58 (1.9%) | 105 (3.4%) |
| 3 months (95% CI) | 18.4 (15.3 - 22.0) | 17.6 (14.8 - 21.1) | 2.6 (1.6 - 4.2) | 5.6 (4.1 - 7.7) |
| 6 months (95% CI) | 14.9 (12.7 - 17.4) | 14.6 (12.5 - 17.0) | 1.9 (1.3 - 3.0) | 4.6 (3.5 - 6.0) |
| 9 months (95% CI) | 13.2 (11.4 - 15.3) | 12.9 (11.2 - 14.8) | 1.7 (1.2 - 2.6) | 4.3 (3.4 - 5.5) |
| 12 months (95% CI) | 12.3 (10.8 - 14.1) | 12.2 (10.6 - 13.9) | 2.0 (1.4 - 2.8) | 3.8 (3.0 - 4.8) |
| 24 months (95% CI) | 10.2 (9.0 - 11.6) | 10.7 (9.5 - 12.0) | 1.8 (1.3 - 2.4) | 3.4 (2.7 - 4.2) |
|  |  |  |  |  |
| **Medications at Time of Outcome** |  |  |  |  |
| Anticoagulant use | 171 (55.2%) | 188 (63.5%) | 23 (39.7%) | 58 (55.2%) |
| Sotalol dose (median [IQR]) | N/A | 160 [160-240] | N/A | 160 [160-240] |
| **AAD: Anti-arrhythmic drug; CI: Confidence interval; IQR: Interquartile range** | | | | |

**Table 3**. Incidence rates of secondary outcomes, by exposure group.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Mortality** | | **Conduction disorders\*** | | **Symptomatic bradycardia#** | | **Bradycardia with pacemaker†** | |
|  | **Dronedarone** | **Sotalol** | **Dronedarone** | **Sotalol** | **Dronedarone** | **Sotalol** | **Dronedarone** | **Sotalol** | |
| **Follow-Up** |  |  |  |  |  |  |  |  | |
| Patient years, total | 3610 | 3251 | 2998 | 2816 | 3581 | 3183 | 3106 | 3106 | |
| Median [IQR] per patient | 0.5 (0.2,1.3) | 0.6 (0.2,1.3) | 0.44 (0.2,1.1) | 0.47 (0.2,1.2) | 0.5 (0.2,1.3) | 0.5 (0.2,1.3) | 0.5 (0.2,1.3) | 0.56 (0.2,1.3) | |
|  |  |  |  |  |  |  |  |  | |
| **Reasons for Censoring by 24 months** |  |  |  |  |  |  |  |  | |
| Occurrence of outcome; n (%) | 75 (2.4%) | 89 (2.9%) | 373 (12.0%) | 397 (12.8%) | 26 (0.84%) | 52 (1.7%) | 23 (0.74%) | 47 (1.5%) | |
| End of data; n (%) | 486 (15.7%) | 499 (16.1%) | 393 (13.0%) | 408 (14.1%) | 485 (15.6%) | 487 (15.7%) | 485 (15.6%) | 487 (15.7%) | |
| Death; n (%) | N/A | N/A | 66 (2.1%) | 75 (2.4%) | 73 (2.4%) | 88 (2.8%) | 73 (2.4%) | 88 (2.8%) | |
| Medication discontinuation; n (%) | 2387 (76.9%) | 2359 (76.0%) | 2146 (69.1%) | 2098 (67.6%) | 2368 (76.2%) | 2322 (74.8%) | 2368 (76.2%) | 2326 (74.9%) | |
| Switched to other AAD; n (%) | 158 (5.1%) | 1588 (5.1%) | 128 (4.1%) | 128 (4.1%) | 154 (5.0%) | 157 (5.1%) | 154 (5.0%) | 158 (5.1%) | |
|  |  |  |  |  |  |  |  |  | |
| **Outcome Incidence (per 100 patient-years)** |  |  |  |  |  |  |  |  | |
| Total; n (%) | 118 (3.8%) | 113 (3.6%) | 418 (13.5%) | 421 (13.6%) | 33 (1.1%) | 56 (1.8%) | 29 (0.93%) | 50 (1.6%) | |
| 3 months (95% CI) | 3.7 (2.5 - 5.5) | 4.2 (2.9 - 6.0) | 27.2 (23.4 - 31.6) | 28.7 (24.9 - 33.1) | 1.8 (1.0 - 3.2) | 3.0 (2.0 - 4.7) | 1.7 (0.9 - 3.0) | 2.7 (1.7 - 4.3) | |
| 6 months (95% CI) | 2.9 (2.1 - 4.1) | 3.6 (2.7 - 4.9) | 22.4 (19.7 - 25.4) | 23.0 (20.4 - 26.1) | 1.6 (1.0 - 2.5) | 2.8 (2.0 - 3.9) | 1.4 (0.8 - 2.3) | 2.5 (1.7 - 3.6) | |
| 9 months (95% CI) | 3.3 (2.5 - 4.4) | 3.6 (2.8 - 4.7) | 20.1 (17.9 - 22.7) | 20.6 (18.4 - 23.1) | 1.3 (0.8 - 2.0) | 2.4 (1.7 - 3.3) | 1.1 (0.7 - 1.8) | 2.1 (1.5 - 3.0) | |
| 12 months (95% CI) | 3.4 (2.6 - 4.3) | 3.7 (2.9 - 4.6) | 19.1 (17.1 - 21.3) | 18.9 (17.0 - 21.1) | 1.2 (0.8 - 1.8) | 2.1 (1.5 - 2.9) | 1.0 (0.6 - 1.6) | 1.9 (1.3 - 2.6) | |
| 24 months (95% CI) | 3.0 (2.4 - 3.8) | 3.4 (2.8 - 4.2) | 16.0 (14.5 - 17.8) | 15.3 (13.8 - 16.9) | 0.9 (0.6 - 1.4) | 1.7 (1.2 - 2.2) | 0.8 (0.5 - 1.2) | 1.5 (1.1 - 2.0) | |
|  |  |  |  |  |  |  |  |  | |
| **Medications at Time of Outcome** |  |  |  |  |  |  |  |  | |
| Anticoagulant use | 44 (37.3%) | 57 (50.4%) | N/A | N/A | N/A | N/A | N/A | N/A | |
| Sotalol dose (median [IQR]) | N/A | 160 [160-240] | N/A | 160 [160-240] | N/A | 160 [160-240] | N/A | 160 [160-240] | |
| **AAD: Anti-arrhythmic drug; CI: Confidence interval; IQR: Interquartile range**  **\*Based on international classification of disease (ICD) or current procedural terminology (CPT) codes for bradycardia, sick sinus syndrome, 2nd or 3rd degree atrioventricular block, or pacemaker insertion**  **#Combination of an inpatient or ambulatory encounter with a primary or secondary ICD code for bradycardia, sick sinus syndrome, or 2nd or 3rd degree AV block within 5 days of an inpatient or ambulatory encounter with an ICD code for syncope or an inpatient or ambulatory encounter with pacemaker insertion**  **†Combination of an inpatient or ambulatory encounter with a primary or secondary ICD code for bradycardia, sick sinus syndrome, or 2nd or 3rd degree AV block within 5 days of an inpatient or ambulatory encounter with pacemaker insertion** | | | | | | | | | |

**Table 4.** Associations of treatment group with primary and secondary outcomes in sensitivity analyses.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Sensitivity Analysis** | **Cardiovascular hospitalization** | | **Ventricular pro-arrhythmia** | | **Mortality** | | **Conduction disorders\*** | | **Symptomatic bradycardia#** | | **Bradycardia with pacemaker†** | |
|  | **HRδ**  **(95% CI)** | **P Value** | **HRδ**  **(95% CI)** | **P**  **Value** | **HRδ**  **(95% CI)** | **P Value** | **HRδ**  **(95% CI)** | **P Value** | **HRδ**  **(95% CI)** | **P Value** | **HRδ**  **(95% CI)** | **P Value** |
| **Primary analysis** | 1.03  (0.88-1.21) | 0.7291 | 0.53  (0.38-0.74) | 0.0002 | 0.89  (0.68-1.16) | 0.3994 | 0.996 (0.87-1.14) | 0.9578 | 0.56  (0.37-0.87) | 0.0079 | 0.56  (0.36-0.89) | 0.0119 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Intention to treat** | 0.998  (0.91-1.1) | 0.9701 | 0.76  (0.64-0.9) | 0.0017 | 0.89  (0.8-0.997) | 0.0377 | 1.08  (0.98-1.19) | 0.1202 | 0.85  (0.66-1.1) | 0.2141 | 0.88  (0.66-1.15) | 0.3731 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| **QT prolongation included in ventricular pro-arrhythmia** | N/A | - | 0.54  (0.39-0.74) | 0.0002 | N/A | - | N/A | - | N/A | - | N/A | - |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Baseline covariate assessment without time limit** | 0.98  (0.84-1.15) | 0.8128 | 0.56  (0.4-0.78) | 0.0007 | 0.88  (0.68-1.15) | 0.3457 | 1.1  (0.96-1.27) | 0.1829 | 0.75  (0.48-1.19) | 0.2160 | 0.75  (0.46-1.22) | 0.2503 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Excluded atrial flutter** | 1.01  (0.84-1.2) | 0.9200 | 0.45  (0.32-0.65) | <0.0001 | 0.84  (0.63-1.11) | 0.2297 | 1.05  (0.91-1.23) | 0.5365 | 0.82  (0.5-1.35) | 0.4419 | 0.84  (0.49-1.43) | 0.5342 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Excluded if recent hospitalization for atrial fibrillation** | 1.15  (0.96-1.38) | 0.1313 | 0.55  (0.39-0.78) | 0.0008 | N/A | - | N/A | - | N/A | - | N/A | - |
| **Include LVEF categorical variable in PSM** | 0.97  (0.83-1.14) | 0.7199 | 0.50  (0.36-0.69) | <0.0001 | N/A | - | N/A | - | N/A | - | N/A | - |
| **Cox proportional hazards with cluster-robust standard errors** | 1.03  (0.88-1.21) | 0.7078 | 0.53  (0.39-0.73) | <0.0001 | 0.89  (0.69-1.15) | 0.3759 | 0.996  (0.87-1.14) | 0.9496 | 0.57  (0.37-0.87) | 0.0095 | 0.56  (0.36-0.89) | 0.0137 |
| **CI: Confidence interval; HR: Hazard ratio, LVEF: Left ventricular ejection fraction, PSM: Propensity score matching**  **\*Based on international classification of disease (ICD) or current procedural terminology (CPT) codes for bradycardia, sick sinus syndrome, 2nd or 3rd degree atrioventricular block, or pacemaker insertion**  **#Combination of an inpatient or ambulatory encounter with a primary or secondary ICD code for bradycardia, sick sinus syndrome, or 2nd or 3rd degree AV block within 5 days of an inpatient or ambulatory encounter with an ICD code for syncope or an inpatient or ambulatory encounter with pacemaker insertion**  **†Combination of an inpatient or ambulatory encounter with a primary or secondary ICD code for bradycardia, sick sinus syndrome, or 2nd or 3rd degree AV block within 5 days of an inpatient or ambulatory encounter with pacemaker insertion**  **δCox proportional hazard regressions among the matched cohorts** | | | | | | | | | | | | |