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ORIGINAL RESEARCH

ATRIAL FIBRILLATION

Dronedarone vs Sotalol Among Patients With Atrial Fibrillation

A Meta-Analysis of Retrospective Observational Databases

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ABSTRACT

BACKGROUND Dronedarone and sotalol are antiarrhythmic drugs (AADs) recommended in similar populations per atrial fibrillation (AF) guidelines; however, comparative safety data are limited.

OBJECTIVES The goal of this study was to assess the safety of dronedarone vs sotalol for treatment of AF in AAD-naive patients.

METHODS This was a prespecified noninterventional meta-analysis of 4 retrospective observational cohort studies from 4 databases (Optum Clinformatics Data Mart, Merative MarketScan, Veterans Health Administration Electronic Health Record, and the Swedish National Patient Register) conducted by using one master protocol. Each analysis emulated the target trial using an active comparator (dronedarone vs sotalol), new user design with an as-treated approach. Primary outcomes were tested hierarchically for dronedarone vs sotalol: first for statistical significance of cardiovascular (CV) hospitalization, and then for statistical significance of ventricular arrhythmias. Propensity score matching (PSM) was used for confounding control, and negative control outcomes were used to assess residual confounding. Outcomes were evaluated by using Cox proportional hazards regression; meta-analysis was performed by using fixed effects models.

RESULTS The dronedarone and sotalol cohorts were well balanced within databases before and after PSM (after PSM mean age range: 62.5-70.9 years; mean CHA_2DS_2-VASc score range: 1.81-3.15). Negative control outcomes exhibited little-to-no evidence of residual confounding. Meta-analysis found significantly lower rates of CV hospitalization (pooled HR: 0.91; 95% CI: 0.85-0.97) and ventricular arrhythmias (pooled HR: 0.77; 95% CI: 0.69-0.85) with dronedarone vs sotalol.

CONCLUSIONS In this retrospective meta-analysis, dronedarone exhibited significantly lower rates of CV hospitalization and ventricular arrhythmias compared with sotalol. These findings provide real-world evidence to support selection of the most appropriate first-line AAD for rhythm control in patients with AF. (JACC Clin Electrophysiol. 2025;11:1531-1542) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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ABBREVIATIONS AND ACRONYMS

AAD = antiarrhythmic drug

AF = atrial fibrillation

FDA = US Food and Drug Administration

HF = heart failure

ICD = International Classification of Diseases

IPCW = inverse probability of censoring weighting

LVEF = left ventricular ejection fraction

MarketScan = Merative MarketScan

NPR = National Patient Register

Optum = Optum Clinformatics Data Mart

pHR = pooled HR

PSM = propensity score matching

RCT = randomized controlled trial

VHA EHR = Veterans Health Administration Electronic Health Record

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia worldwide, and its prevalence is increasing.[1,2] Antiarrhythmic drugs (AADs), a recommended rhythm control treatment for paroxysmal and persistent AF, are associated with increased risk of adverse events, including arrhythmias (bradyarrhythmias and ventricular tachyarrhythmia) and increased mortality.[3] Current American College of Cardiology/American Heart Association/American College of Clinical Pharmacy/Heart Rhythm Society and European Society of Cardiology AF guidelines underscore the importance of safety first when choosing an AAD for rhythm control in patients with nonpermanent AF.[4,5]

Dronedarone and sotalol are recommended for similar populations by the American College of Cardiology/American Heart Association/American College of Clinical Pharmacy/Heart Rhythm Society AF guidelines.[5] Both medications have class III properties with class II antiadrenergic rate effects with similar limitations for use in patients with heart failure (HF), sick sinus syndrome, atrioventricular block, or existing QT prolongation warranting postmarketing comparative safety analysis.[5] No randomized controlled trial (RCT) exists directly comparing the safety of dronedarone and sotalol in patients with AF. Evidence to date has included indirect comparisons from RCTs, between dronedarone and other AADs, or real-world evidence observational studies limited by sample size or low rates of events of interest.[6-11]

The aim of the current study was to address these limitations by using a prespecified, fixed-effects meta-analysis of 4 large observational databases executed by using one master protocol. The study emulated the hypothetical target RCT and had sufficient power to detect significant differences on clinically relevant safety events between dronedarone and sotalol in patients with AF. A fixed-effects model is appropriate when there are <5 studies in a meta-analysis and no significant heterogeneity is observed.[12,13] Primary objectives were assessed sequentially in the order of: 1) cardiovascular (CV) hospitalization event rates; and 2) rate of ventricular arrhythmias among AAD-naive patients with AF newly initiating dronedarone vs sotalol.

METHODS

STUDY DESIGN. This study was a prespecified, noninterventional, fixed-effects meta-analysis of 4 retrospective observational cohort studies derived from 4 databases (Optum Clinformatics Data Mart [Optum], Merative MarketScan [MarketScan], Veterans Health Administration Electronic Health Record [VHA EHR], and the Swedish National Patient Register [NPR]) conducted using one master protocol (Supplemental Methods). Each analysis emulated the hypothetical target trial using an active comparator, new user design with an as-treated approach to assess the comparative safety of dronedarone vs sotalol for treatment of AF in AAD-naive patients, as these methods most closely emulate an RCT.[14-16] All data came from Health Insurance Portability and Accountability Act-compliant real-world data sources. The Stanford Institutional Review Board provided ethical approval for the use of VHA EHR data. The Swedish Ethical Review Authority approved the use of the Swedish NPR.

PARTICIPANTS. Full inclusion and exclusion criteria are included in the Supplemental Methods 1.3 and 1.4. Patients were included if they had ≥1 prescription claim for dronedarone or sotalol between January 1, 2012 (January 1, 2013, for the Swedish NPR), and 6 months before the end of data to allow for 6 months of potential follow-up (patients could be censored before 6 months of follow-up); end of data, Optum: April 30, 2022; MarketScan: June 20, 2021; VHA EHR: June 30, 2021; Swedish NPR: December 31, 2015.

The first outpatient prescription claim for dronedarone or sotalol was considered the index date. Patients were required to have an AF diagnosis and no history of class I or III AAD use. The patient's AF diagnosis was required to occur in the 6 months before or on the index date in the US databases only.

Specific exclusion criteria included cancer, second- or third-degree atrioventricular block, ventricular arrhythmias, or insertion of a pacemaker, implantable cardioverter-defibrillator, or cardiac resynchronization therapy defibrillator at any time before the index date. Patients with a non-recommended average daily

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sotalol dose on the index date (<160 mg, measurable in U.S. databases only) were excluded to remove patients prescribed a dose with subtherapeutic class III antiarrhythmic effects.[17]

Follow-up was defined as the index date until the earliest of disenrollment/loss of benefits eligibility, death, discontinuation of index AAD, addition of any class I or III AAD, occurrence of an outcome, or end of available data.

OUTCOMES. Primary outcomes included CV hospitalization and ventricular arrhythmias separately. CV hospitalization was defined as an inpatient claim with an International Classification of Diseases (ICD) diagnosis code for myocardial infarction, stroke, transient ischemic attack, HF, or AF. Ventricular arrhythmias were defined as ICD diagnoses for ventricular fibrillation and flutter, ventricular tachycardia, torsade de pointes, re-entry ventricular arrhythmia, or cardiac arrest (Supplemental Methods 1.5.2).

Secondary outcomes included all-cause mortality (VHA EHR and Swedish NPR only), composite of all-cause mortality and ventricular arrhythmias, and bradyarrhythmias associated with syncope/pacemaker implant (Supplemental Methods 1.5.2).

EXPOSURE. Continuous exposure to the index AAD was defined as days' supply of the index medication with an allowable gap of ≤30 consecutive days (Supplemental Methods).

COVARIATES. Covariates related to demographic characteristics, AF diagnosis history, index AAD, health care resource utilization, comorbidities, and concomitant therapies were defined through diagnostic, procedure, and medication codes. These covariates were used in propensity score matching (PSM) (Supplemental Methods 1.5.3).

STATISTICAL ANALYSIS. A stepwise approach assessed baseline equipoise and ensured no evidence of residual confounding before assessing comparative outcomes (Supplemental Methods 1.9.2). Each cohort was matched via PSM using a 1:1 ratio with a 0.03 caliper and a priori selected covariates. Baseline equipoise was defined as a standardized difference <0.1 between cohorts for ≥90% of PSM covariates. Residual confounding was assessed via a negative control outcome defined similarly in prior studies (composite of hip fractures, cancer, and infections) using Cox proportional hazards regression.[10,18] A secondary negative control outcome of incident diabetes, pneumonia, fall accidents, incident osteoarthritis, and incident chronic obstructive pulmonary disease was assessed in the Swedish cohort.[19]

Outcomes in the database-specific cohorts were analyzed. Propensity score–adjusted HRs and 95% CIs were estimated by using Cox proportional hazards regression (Supplemental Methods 1.9.2). For covariates in the PS model, missing indicator variables were generated to capture missing or unknown values. Incidence rates of outcomes per 100 person-years were also reported. E-values, which estimate the magnitude of confounding needed to explain away the observed effect, were estimated for each primary outcome HR.[20]

Hypothesis testing was performed at the meta-analysis level for the primary outcome using a hierarchical approach: first, heterogeneity between database-specific HRs for CV hospitalization was assessed by using the I^2 statistic and P value from the Cochran Q test, with $P < 0.10$ considered significant heterogeneity. If no significant heterogeneity was identified, HRs for CV hospitalization were pooled by using a fixed-effects model and tested for statistical significance. If a statistically significant difference was observed for dronedarone vs sotalol for rates of CV hospitalization, heterogeneity and statistical significance for rates of ventricular arrhythmias were tested for dronedarone vs sotalol.

Meta-analysis was conducted for the secondary outcomes, without hypothesis testing; individual HRs were pooled by using a fixed-effects model.

Sensitivity analyses were conducted in each analysis, when appropriate, and at the meta-analysis level to assess the robustness of the results. Priority sensitivity analyses are described in the following paragraph and in the Supplemental Methods 1.9.4. Because out-of-pocket cost and side effects may function as barriers to persistence on AAD therapy, a sensitivity analysis was conducted in which outcomes were assessed among patients with ≥180 days of follow-up, and separately ≥365 days of follow-up. The US Food and Drug Administration (FDA) prescribing information recommends inpatient initiation of sotalol due to increased risk of ventricular proarrhythmia.[17] However, inpatient administration of medications is not captured in claims databases; as a result, patients entered the cohort on the first outpatient prescription claim. A sensitivity analysis excluding patients with an AF-related hospitalization in the week before the index date was conducted in the US databases to exclude patients initiating sotalol in the inpatient setting to address this potential time-zero bias.

Finally, 2 post hoc sensitivity analyses were conducted. The first was designed to address potential informative censoring in the Optum and MarketScan analyses, given the differential follow-up times and discontinuation rates between cohorts. Inverse probability of censoring weighting (IPCW) was

TABLE 1 Demographic and Clinical Characteristics Post-Propensity Score Matching

	Optum (n = 8,373)			MarketScan (n = 10,754)		
	Dronedarone	Sotalol	ASD	Dronedarone	Sotalol	ASD
Follow-up time, y[a,b]						
Mean ± SD	0.59 ± 0.90	0.90 ± 1.17	NA	0.58 ± 0.89	0.81 ± 1.06	NA
Median (Q1-Q3)	0.25 (0.08-0.69)	0.45 (0.15-1.16)		0.25 (0.08-0.68)	0.39 (0.14-1.05)	
Demographic characteristics						
Age, continuous, y[c]						
Mean ± SD	68.40 ± 10.74	68.44 ± 10.71	0.004	62.56 ± 11.43	62.51 ± 11.27	0.004
Sex						
Male	4,558 (54.4)	4,526 (54.1)	0.008	6,705 (62.3)	6,772 (63.0)	0.013
Female	3,815 (45.6)	3,847 (45.9)		4,049 (37.7)	3,982 (37.0)	
Race/ethnicity						
White	6,486 (77.5)	6,518 (77.8)	0.011	NA	NA	NA
African American	632 (7.5)	612 (7.3)		NA	NA	
Hispanic	661 (7.9)	649 (7.8)		NA	NA	
Other/unknown/missing	594 (7.1)	594 (7.1)		NA	NA	
Clinical characteristics						
Time between the first diagnosis of AF and the index date, mo						
Mean ± SD	2.17 ± 2.02	2.17 ± 2.06	0.002	1.90 ± 1.94	1.88 ± 1.97	0.012
CHA_2DS_2-VASc score[a]						
Mean ± SD	3.14 ± 1.83	3.15 ± 1.82	0.004	2.28 ± 1.79	2.26 ± 1.75	0.007
Median (Q1-Q3)	3.00 (2.00-4.00)	3.00 (2.00-4.00)		2.00 (1.00-3.00)	2.00 (1.00-3.00)	
Cardiomyopathy or congenital anomalies of the heart	1,235 (14.7)	1,227 (14.7)	0.003	1,279 (11.9)	1,263 (11.7)	0.005
Chronic renal disease	1,240 (14.8)	1,248 (14.9)	0.003	649 (6.0)	660 (6.1)	0.004
Congestive heart failure	1,526 (18.2)	1,517 (18.1)	0.003	1,297 (12.1)	1,289 (12.0)	0.002
Diabetes mellitus	2,227 (26.6)	2,238 (26.7)	0.003	2,364 (22.0)	2,358 (21.9)	0.001
Hypertension	6,470 (77.3)	6,464 (77.2)	0.002	7,036 (65.4)	7,041 (65.5)	0.001
Ischemic heart disease	3,263 (39.0)	3,235 (38.6)	0.007	3,282 (30.5)	3,286 (30.6)	0.001
Baseline therapy use						
Ablation procedure	29 (0.3)	30 (0.4)	0.002	31 (0.3)	32 (0.3)	0.002
Time since last cardioversion						
No previous cardioversion	6,653 (79.5)	6,668 (79.6)	0.007	8,294 (77.1)	8,279 (77.0)	0.014
Cardioversion within previous 2 days	409 (4.9)	415 (5.0)		702 (6.5)	739 (6.9)	
Cardioversion >2 days before	1,311 (15.7)	1,290 (15.4)		1,758 (16.3)	1,736 (16.1)	
Anticoagulants	4,324 (51.6)	4,344 (51.9)	0.005	4,886 (45.4)	4,892 (45.5)	0.001
Digoxin	494 (5.9)	489 (5.8)	0.003	739 (6.9)	713 (6.6)	0.010
Beta-blocking agents	5,321 (63.5)	5,312 (63.4)	0.002	6,552 (60.9)	6,510 (60.5)	0.008
Calcium-channel blockers	3,045 (36.4)	3,083 (36.8)	0.009	3,730 (34.7)	3,685 (34.3)	0.009

Values are n (%) unless otherwise indicated. [a]Denotes characteristic not included in the propensity score. [b]Follow-up time was measured for each outcome, accounting for censoring due to occurrence of outcome. Follow-up time presented is for cardiovascular hospitalization. [c]Age is reported here as a continuous variable but was included in the propensity score as a categorical variable (Supplemental Methods 1.5.2).

AF = atrial fibrillation; ASD = absolute standardized difference; MarketScan = Merative MarketScan database; NA = not assessed; NPR = National Patient Register; Optum = Optum Clinformatics Data Mart database; VHA EHR = Veterans Health Administration Electronic Health Record.

Continued on the next page

implemented as defined in Young et al[21] (Supplemental Methods 1.9.5). To address the potential for imbalance in left ventricular ejection fraction (LVEF) between cohorts, a second sensitivity analysis with categorical variables for LVEF was conducted for the primary outcomes in the VHA analyses.

Database-specific analyses were performed by using the Aetion Evidence Platform (Aetion, Inc), SAS (SAS Institute, Inc), or Stata (StataCorp). Meta-analyses were performed on the Aetion Evidence Platform. A P value <0.05 was considered statistically significant.

RESULTS

Across the 4 databases, 27,955 patients initiating dronedarone and 35,647 patients initiating sotalol were identified (Supplemental Tables 1 and 2). After PSM, 23,275 patients remained in each cohort.

TABLE 1 Continued

VHA EHR (n = 3,106)			Swedish NPR (n = 1,042)		
Dronedarone	**Sotalol**	**ASD**	**Dronedarone**	**Sotalol**	**ASD**
1.1 ± 1.5	1.0 ± 1.2	NA	0.87 ± 0.68	0.86 ± 0.70	NA
0.5 (0.2-1.2)	0.5 (0.2-1.3)		0.71 (0.28-1.28)	0.70 (0.22-1.26)	
Demographic characteristics					
70.9 ± 10.2	70.9 ± 10.2	0.003	65.1 ± 10.2	65.8 ± 10.2	0.069
3,030 (97.6)	3,031 (97.6)	0.002	602 (57.8)	625 (60.0)	0.045
76 (2.5)	75 (2.4)		440 (42.2)	417 (40.0)	
2,857 (92.0)	2,852 (91.8)	0.076	NA	NA	NA
176 (5.7)	166 (5.3)		NA	NA	
3 (0.10)	6 (0.19)		NA	NA	
70 (2.3)	82 (2.6)		NA	NA	
Clinical characteristics					
2.24 ± 1.97	2.28 ± 2.09	0.02	NA	NA	NA
2.00 ± 1.29	1.98 ± 1.28	0.024	1.84 ± 1.44	1.81 ± 1.30	0.020
2.00 (1.00-3.00)	2.00 (1.00-3.00)		2.00 (1.00-3.00)	2.00 (1.00-3.00)	
192 (6.2)	184 (5.9)	0.011	36 (3.5)	28 (2.7)	0.044
274 (8.8)	260 (8.4)	0.016	14 (1.3)	14 (1.3)	0.000
311 (10.0)	297 (9.6)	0.015	113 (10.8)	88 (8.4)	0.081
881 (28.4)	889 (28.6)	0.006	120 (11.5)	108 (10.4)	0.037
1,997 (64.3)	2,026 (65.2)	0.011	597 (57.3)	578 (55.5)	0.037
1,270 (40.9)	1,277 (41.1)	0.005	96 (9.2)	98 (9.4)	0.007
Baseline therapy use					
15 (0.48)	15 (0.48)	0.000	28 (2.7)	29 (2.8)	0.006
2,943 (94.8)	2,962 (95.4)	0.028	721 (69.2)	681 (65.4)	0.138
32 (1.0)	35 (1.0)		92 (8.8)	47 (4.5)	
138 (4.4)	116 (3.7)		229 (22.0)	314 (30.1)	
1,654 (53.3)	1,673 (53.9)	0.012	779 (74.8)	809 (77.6)	0.068
132 (4.3)	148 (4.8)	0.025	111 (10.7)	106 (10.2)	0.016
1,531 (49.3)	1,506 (48.5)	0.016	888 (85.2)	893 (85.7)	0.014
862 (27.8)	875 (28.2)	0.009	245 (23.5)	238 (22.8)	0.016

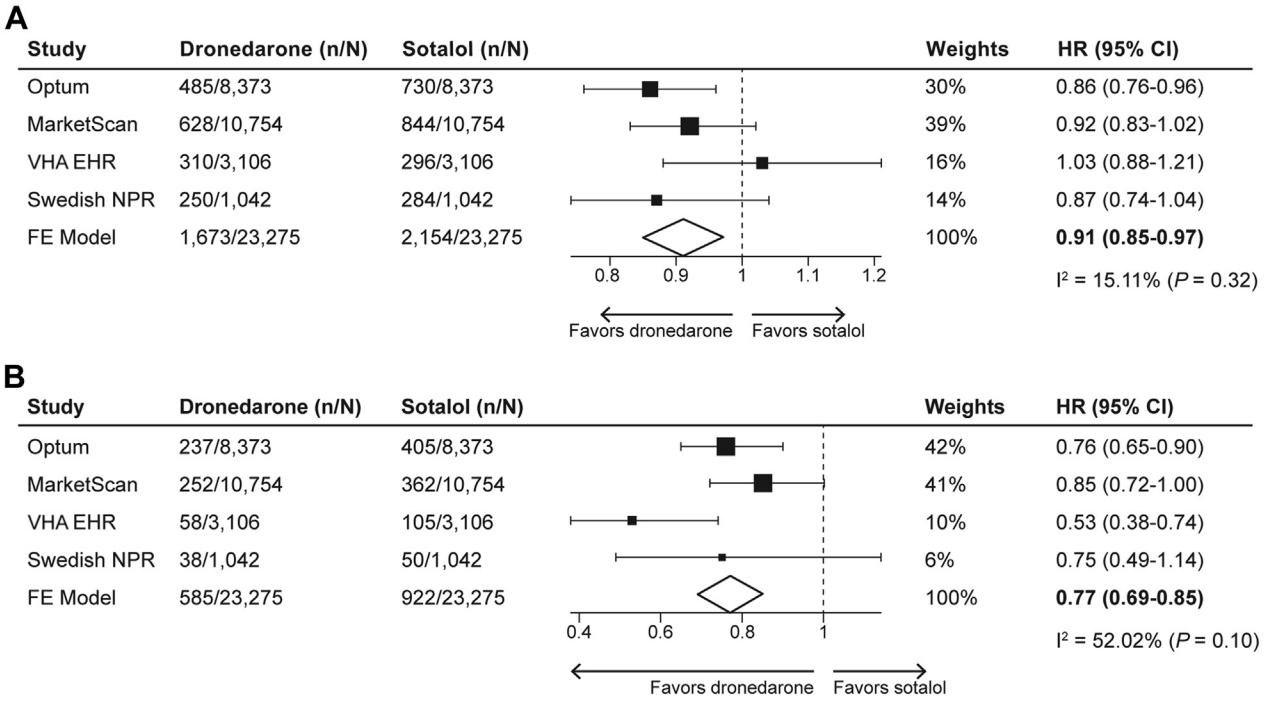
Demographic and baseline characteristics were overall balanced between cohorts (**Table 1**), with equipoise achieved in all US analyses and a small imbalance (4 of 29 PSM covariates) in the Swedish NPR analysis. The median age and sex distributions were comparable between the 4 databases, except for the VHA EHR, in which most patients were male (Supplemental Tables 3 and 4, **Table 1**).

Mean ± SD CHA_2DS_2-VASc score (Supplemental Table 4) in the dronedarone vs sotalol cohort was highest in Optum (3.14 ± 1.83 vs 3.15 ± 1.82), followed by MarketScan (2.28 ± 1.79 vs 2.26 ± 1.75), VHA EHR (2.00 ± 1.29 vs 1.98 ± 1.28), and the Swedish NPR (1.84 ± 1.44 vs 1.81 ± 1.30). The median (Q1-Q3) sotalol dose at index was 160 mg (160-160 mg) in all 3 US analyses (dosage data were unavailable in the Swedish NPR). The median (Q1-Q3) dronedarone dose at index was 800 mg (800-800 mg) in the Optum, MarketScan, and VHA EHR databases.

The negative control outcomes suggested little-to-no evidence of residual confounding based on nonsignificant HRs (Optum: 0.95 [95% CI: 0.80-1.12]; MarketScan: 1.10 [95% CI: 0.92-1.30]; VHA EHR: 0.89 [95% CI: 0.78-1.03]; and Swedish NPR: 1.03 [95% CI: 0.73-1.49]).

Dronedarone, compared with sotalol, significantly reduced the risk of CV hospitalization (pooled HR [pHR]: 0.91; 95% CI: 0.85-0.97; $P < 0.01$) with low

FIGURE 1 Outcomes of CV Hospitalization and Ventricular Arrhythmias



Database-specific HRs and pooled HRs for the outcome of cardiovascular (CV) hospitalization (A) and ventricular arrhythmias (B) for propensity score–matched patients with atrial fibrillation (AF) newly initiating dronedarone vs sotalol in the outpatient setting. FE model = fixed-effects (pooled) model; MarketScan = Merative MarketScan database; NPR = National Patient Register; Optum = Optum Clinformatics Data Mart database; VHA EHR = Veterans Health Administration Electronic Health Record.

heterogeneity between databases (Figure 1A). Among patients taking sotalol who had available dose information, the median (Q1-Q3) daily dose at the time of a CV hospitalization was 160 mg (160-240 mg) in each US analysis. CV hospitalization incidence rates were similar between dronedarone and sotalol arms at 24 months' postindex within each database (Supplemental Table 5).

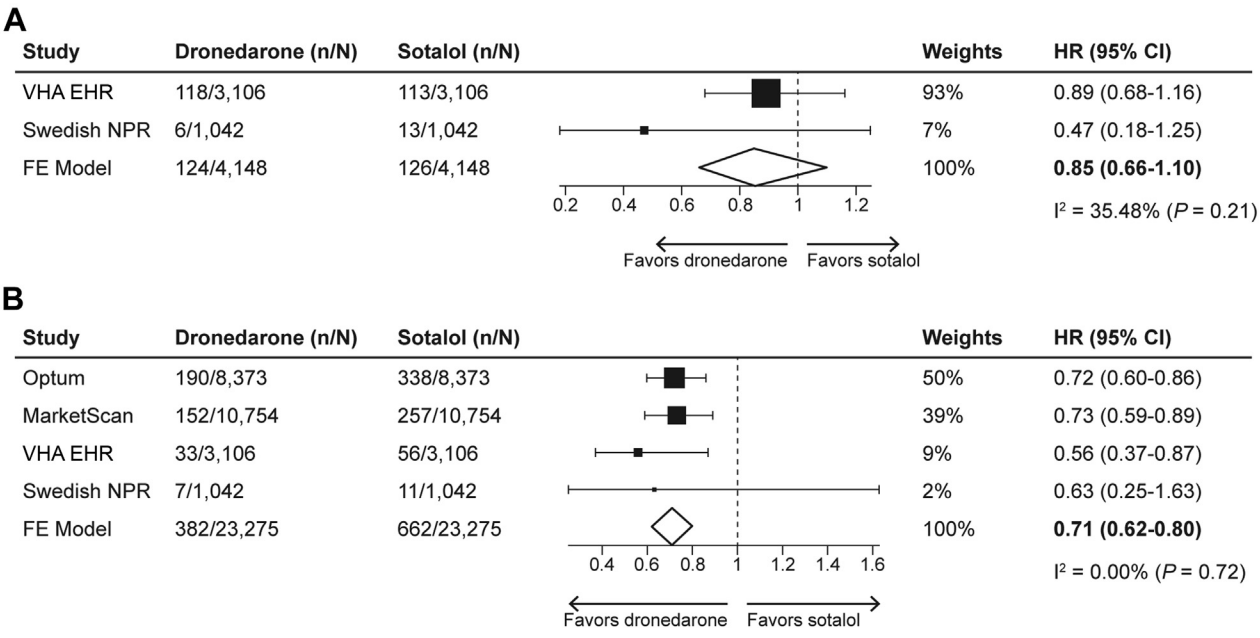
Dronedarone, compared with sotalol, significantly reduced the risk of ventricular arrhythmias (pHR: 0.77; 95% CI: 0.69-0.85; $P < 0.01$) with moderate but nonsignificant heterogeneity between databases (Figure 1B). Among patients taking sotalol, the median (Q1-Q3) dose at the time of a ventricular arrhythmia event was 160 mg (160-240 mg) in each US analysis. Incidence rates for ventricular arrhythmias were lower for dronedarone-treated than sotalol-treated patients at 24 months' postindex in the Optum, VHA EHR, and Swedish NPR databases (Supplemental Table 5).

All-cause mortality assessed in the VHA EHR and Swedish NPR databases indicated a trend toward lower mortality rates in the dronedarone cohort (pHR: 0.85; 95% CI: 0.66-1.10) (Figure 2A). The median (Q1-Q3) sotalol dose at the time of mortality was 160 mg (160-240 mg) for VHA EHR patients taking sotalol. A composite endpoint of all-cause mortality and ventricular arrhythmias assessed in the VHA EHR and Swedish NPR showed consistency with both individual endpoints (pHR: 0.72; 95% CI: 0.60-0.86). Compared with sotalol, dronedarone use posed a lower risk of bradyarrhythmias associated with syncope/pacemaker implant (pHR: 0.71; 95% CI: 0.62-0.80) across all databases (Figure 2B). Incidence rates of bradyarrhythmias associated with syncope/pacemaker implant were lower for dronedarone-treated than sotalol-treated patients at 24 months' postindex in the Optum, MarketScan, and VHA EHR databases (Supplemental Table 5).

For CV hospitalization and ventricular arrhythmias, E-values indicated it was unlikely that an unmeasured confounder would explain away the effect estimates (1.11 to 1.60 for CV hospitalization and 1.63 to 3.18 for ventricular arrhythmia).

In a sensitivity analysis of patients with a minimum of 180 or 365 days of follow-up, a lower HR for

FIGURE 2 Outcomes of All-Cause Mortality and Bradyarrhythmias Associated With Syncope/Pacemaker Implant



Database-specific HR and pooled HRs for the outcome of all-cause mortality (A) and bradyarrhythmias (B) associated with syncope/pacemaker implant for propensity score–matched patients with atrial fibrillation newly initiating dronedarone vs sotalol in the outpatient setting. Abbreviations as in Figure 1.

CV hospitalization was observed for dronedarone vs sotalol, compared with the primary analysis (Table 2). The HR for ventricular arrhythmias in the minimum-180-day analysis was similar to the HR in the primary analysis but less pronounced in the minimum-365-day analysis. In an analysis excluding patients with recent AF hospitalization, the treatment effect for CV hospitalization was closer to the null compared with the primary analysis and was unchanged for ventricular arrhythmias. Results of the US database-specific IPCW analysis were similar to those of the primary analysis for the endpoints of CV hospitalization and ventricular arrhythmias. For the sensitivity analysis, including the categorical LVEF variable in the PSM for the VHA analysis, the results were similar to those of the primary analysis. Results of additional sensitivity analyses are presented in Supplemental Table 6.

The study is summarized in the **Central Illustration**.

DISCUSSION

This study is the first prespecified meta-analysis across multiple databases comparing the safety of 2 AADs indicated for similar patients with comparable AF disease states and employing an active comparator, new user design with a target-trial approach. This approach, using one master protocol, resulted in large cohorts, well-balanced comparator arms, no significant difference in negative control analyses that would suggest residual confounding, consistently robust findings across databases, and E-values indicating that an unknown confounder would be unlikely to explain the primary effect estimates. The current study shows that dronedarone is associated with statistically significant lower rates of CV hospitalization and ventricular arrhythmias compared with sotalol, with a trend toward reduced mortality and bradyarrhythmias associated with syncope/pacemaker implant.

Although limited, the evidence from a recently published network meta-analysis[11] supports the current findings. In addition, a real-world study of AAD-naive South Korean adults found that dronedarone-treated patients had a significantly lower hazard of CV hospitalization than sotalol-treated patients (HR: 0.62; 95% CI: 0.53-0.72).[6] Results from related but not directly comparable studies found a lower hazard for CV hospitalization, or its components, for patients receiving dronedarone compared with sotalol (or other AADs, including sotalol).[7-9] Findings are consistent with ATHENA (A PlaceboControlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular

TABLE 2 Sensitivity Analysis Effect Estimates for Outcomes of CV Hospitalization and Ventricular Arrhythmias

		HR (95% CI)	
	Database	CV Hospitalization	Ventricular Arrhythmias
Primary analysis	All databases	0.91 (0.85-0.97)	0.77 (0.69-0.85)
Minimum of 180 days' follow-up required	All databases	0.81 (0.73-0.89)	0.75 (0.65-0.87)
Minimum of 365 days' follow-up required	All databases	0.74 (0.66-0.84)	0.82 (0.68-0.98)
Excluding patients with recent AF hospitalization	All databases	0.98 (0.90-1.06)	0.77 (0.68-0.88)
Primary analysis	Optum	0.86 (0.76-0.96)	0.76 (0.65-0.90)
IPCW analysis	Optum	0.83 (0.74-0.94)	0.74 (0.63-0.87)
Primary analysis	MarketScan	0.92 (0.83-1.02)	0.85 (0.72-1.00)
IPCW analysis	MarketScan	0.92 (0.82-1.02)	0.85 (0.72-1.00)
Primary analysis	VHA EHR	1.03 (0.88-1.21)	0.53 (0.38-0.74)
LVEF included in PSM	VHA EHR	0.97 (0.83-1.14)	0.50 (0.36-0.69)

CV = cardiovascular; IPCW = inverse probability of censoring weighting; LVEF = left ventricular ejection fraction; PSM = propensity score matching; other abbreviations as in Table 1.

Hospitalization or Death from any Cause in Patients with Atrial Fibrillation/Atrial Flutter), which found a lower hazard of CV hospitalization among patients taking dronedarone compared with placebo (HR: 0.74; 95% CI: 0.67-0.82; $P < 0.001$).[22]

The current study establishes that dronedarone significantly reduces the risk of ventricular arrhythmias compared with sotalol. Although few comparable published studies exist,[3,8] some parallels can be drawn. A South Korean study reported a significantly lower risk for ventricular tachyarrhythmia in patients taking dronedarone vs sotalol (HR: 0.04; 95% CI: 0.00-0.40),[6] although ventricular tachyarrhythmia is more limited than proarrhythmia. A Swedish study reported a lower but nonsignificant risk in patients taking dronedarone vs sotalol over all available follow-up (HR: 0.58; 95% CI: 0.33-1.04) for ventricular fibrillation/ventricular tachycardia.[10] The lower rates of ventricular arrhythmias observed with dronedarone vs sotalol in the current study may have occurred because of: 1) lower proarrhythmic effects with dronedarone[23]; 2) a potentially greater benefit with dronedarone for reducing ventricular arrhythmias in this population (which has a high prevalence of CV risk factors and disease) as reported in the ATHENA trial; or 3) the class IV effects of dronedarone on slow-release calcium channels, similar to amiodarone. Class IV effects would reduce early and delayed afterdepolarizations, transmural dispersion of repolarization, and early afterdepolarization-induced triggered activity, all known causes of ventricular arrhythmias, as shown in canine models.[23,24] The lower risk of ventricular arrhythmias with dronedarone may also reflect the risk for torsade de pointes and other potentially lethal proarrhythmias resulting from the effect of class III AADs such as sotalol and dofetilide on potassium channels.[3,25]

The pHRs for all-cause mortality and a composite endpoint of all-cause mortality and ventricular arrhythmias were directionally in favor of dronedarone compared with sotalol, consistent with the lower risk of potentially life-threatening ventricular arrhythmias. Previous studies, although not directly comparable, have identified lower rates of all-cause mortality for patients taking dronedarone compared with sotalol.[6,10] The Swedish study found a lower hazard of all-cause mortality for dronedarone vs sotalol (HR: 0.44; 95% CI: 0.34-0.57),[10] as did the South Korean study (HR: 0.88; 95% CI: 0.41-1.91).[6] A US study estimated a lower hazard of all-cause death for dronedarone compared with other AADs, including amiodarone, dofetilide, flecainide, propafenone, and sotalol (HR: 0.66; 95% CI: 0.41-1.05).[7]

The pHR for bradyarrhythmias associated with syncope/pacemaker implant was numerically lower for dronedarone compared with sotalol, likely due to the adverse class II effects of sotalol. In a South Korean study, patients with AF receiving dronedarone, vs those receiving sotalol, had a lower hazard of conduction disorders and arrhythmias (composite outcome), although the outcomes in the South Korean study were defined differently than those in the current study (HR: 0.59; 95% CI: 0.49-0.70).[6]

Across primary outcomes, the median sotalol dose at the time of event was 160 mg/d, indicating that the lowest recommended therapeutic sotalol dose in the presence of normal renal function still carried a significantly increased risk of potential adverse class II (bradyarrhythmias associated with syncope/pacemaker implant) and class III (ventricular proarrhythmia) events compared with dronedarone with an inferior effect on CV hospitalization. Although higher doses of sotalol may improve efficacy and decrease CV hospitalization, class II and III proarrhythmic adverse events could possibly be expected to increase.

The results from the sensitivity analyses exhibited robust findings as they were generally consistent with the primary results. When follow-up was truncated to 180/365 days, findings were similar to those of the main analyses. However, trends in the pHR varied based on the outcome, likely due to the selection of healthier patients who were better able to tolerate or afford treatment and thus stay on treatment. Furthermore, the impact of these study design modifications is likely differential with respect to treatment group and database, considering the different follow-up times and insurance coverage.

CENTRAL ILLUSTRATION Dronedarone Versus Sotalol Among Patients With Atrial Fibrillation: *A Meta-Analysis of Retrospective Observational Databases*

Study Population

AAD-naive individuals with AF treated with dronedarone or sotalol

Study Design

4 retrospective observational cohort studies derived from 4 databases; dronedarone patients PSM 1:1 with sotalol patients

Optum, n = 8,373/arm
Merative MarketScan, n = 10,754/arm
VHA EHR, n = 3,106/arm
Swedish NPR, n = 1,042/arm

Pre-Specified Meta-Analysis

Fixed effects model

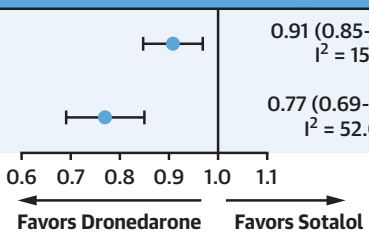
N = 23,275/arm
Primary and secondary outcomes assessed

Index date 1st claim

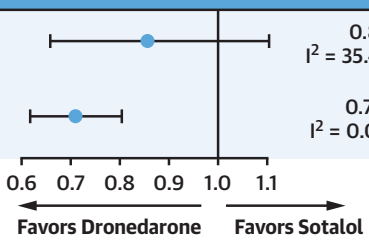
–180 days enrollment assessment period | Day 0 | Follow-up until censored or end of data

Results: Fixed Effects Model

Primary Outcomes	Dronedarone, n/N (%)	Sotalol, n/N (%)	pHR (95% CI; *P* Value)
CV Hospitalization	1,673/23,275 (7.2)	2,154/23,275 (9.3)	0.91 (0.85-0.97; *P* < 0.01) I^2 = 15.11% (*P* = 0.32)
Ventricular Arrhythmias	585/23,275 (2.5)	922/23,275 (4.0)	0.77 (0.69-0.85; *P* < 0.01) I^2 = 52.02% (*P* = 0.10)



Secondary Outcomes	Dronedarone, n/N (%)	Sotalol, n/N (%)	pHR (95% CI)
All-Cause Mortality	124/4,148 (3.0)	126/4,148 (3.0)	0.85 (0.66-1.10)[a] I^2 = 35.48% (*P* = 0.21)
Bradyarrhythmias Associated With Syncope/ Pacemaker Implant	382/23,275 (1.6)	662/23,275 (2.8)	0.71 (0.62-0.80)[a] I^2 = 0.00% (*P* = 0.72)



I^2 is a statistical measure of study heterogeneity; the *P* value tests the overall significance of heterogeneity.
[a]Only the primary endpoints were tested statistically, therefore, there are no *P* values for the secondary endpoints.

Limitations

- No data from RCTs
- Patients who received <160 mg/day sotalol or those who initiated sotalol as inpatients and discontinued during hospital stay were excluded
- Could not distinguish cause for CV hospitalization (AE or non-responder)
- Different follow-up times and reasons for censoring between treatment arms in the Optum and MarketScan databases

Conclusions

Compared with sotalol, dronedarone demonstrated:

- Statistically significant lower rate of CV hospitalization (*P* < 0.01)
- Statistically significant lower rate of ventricular arrhythmias (*P* < 0.01)
- Numerically lower rate of bradyarrhythmias associated with syncope/pacemaker implant

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AAD = antiarrhythmic drug; AE = adverse event; AF = atrial fibrillation; CV = cardiovascular; pHR = pooled HR; NPR = National Patient Register; PSM = propensity score matched; RCTs = randomized controlled trials; VHA EHR = Veterans Health Administration Electronic Health Record.

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Given that the US FDA prescribing information recommends inpatient sotalol initiation,[17] patients with an AF hospitalization in the week before the index date were excluded as a sensitivity analysis, removing more sickly patients with AF from the analytic cohort. The results for ventricular arrhythmias were consistent with the results of the primary analyses despite removing more vulnerable patients at risk of ventricular proarrhythmia, particularly for patients taking sotalol per labeling recommendation, whereas the pHR for CV hospitalization increased toward the null.

This study has several strengths. First, it included a meta-analysis specified a priori of 4 individual analyses using large, population-based, diverse databases, and it featured consistent methods from one protocol with little adaptation. Second, the study used an active comparator, new user, target-trial design, which improves the validity of study findings and follows FDA real-world evidence guidance.[26-28] Third, each study included negative control outcomes and E-value estimates as part of the bias assessments to ascertain the robustness of our findings.[20] Fourth, the findings are generally robust across sensitivity analyses that were designed to address the impact of various assumptions in the main analyses. Lastly, because medication use in the trial setting often differs from patterns observed in practice settings, this study can provide insights into the real-world use and safety risks in a broader population.

STUDY LIMITATIONS. Given the real-world nature of this study, treatment was not randomized and is thus susceptible to confounding by indication. However, the active comparator, new user design coupled with PSM was used to adjust for covariates and address measured and unmeasured confounding, including confounding by indication. Furthermore, demographic and baseline covariates were well balanced before and after PSM.

Currently, no specific *ICD* codes for AF recurrence exist, and measures of AF burden cannot be evaluated through EHR. We therefore used the endpoint of CV hospitalization, which is reflective of hospitalizations with primary diagnoses of HF, myocardial infarction, or AF.[22,29] For the endpoint of CV hospitalization, we are unable to distinguish between hospitalizations due to adverse safety events and those resulting from treatment nonresponse.

ICD-Ninth Revision codes cannot differentiate between AF type (ie, persistent vs permanent). In addition, ICD-Tenth Revision codes for AF subtypes are used inconsistently, and the validity of using them to classify patients into AF subtypes is uncertain.[30] However, we have included these classifications of AF in the PSM model because the classification in the database could possibly represent different patient phenotypes (eg, those classified with permanent AF may have more AF burden or more severe heart disease than those not classified as such).

To ensure that the population did not include individuals who were potentially treated off-label, patients with a recent hospitalization for HF were excluded, which could potentially reduce the overall number of comorbidities within the captured sample.

The sotalol cohort is a selected one as patients were excluded who initiated in the inpatient setting and discontinued during the hospitalization because of an adverse event. In a previous study, an estimated 17.5% of patients initiating sotalol as an inpatient were found to discontinue/change therapy due to adverse events, mainly related to class II and III properties.[31] Thus, this study likely underestimates the true event rates for ventricular arrhythmias and bradyarrhythmias associated with syncope/pacemaker implant in this sotalol "survivor" cohort. In addition, this study excluded patients in the United States whose daily sotalol dose was subtherapeutic for AF treatment (<160 mg) on the index date. This could potentially exclude some patients more susceptible to class III effects, whose sotalol dose had been reduced because of a comorbidity such as renal impairment. Because claims data do not include information on creatinine levels or glomerular filtration rate, we were unable to account for sotalol dose adjustments based on creatinine clearance.

Different follow-up times and reasons for censoring were observed between arms in the Optum and MarketScan databases. To address potential informative censoring, post hoc analyses were performed by using IPCW. The relatively consistent results may suggest reliability of the primary results or may indicate that informative censoring could not be sufficiently addressed.

CONCLUSIONS

This meta-analysis of retrospective observational databases shows that patients with AF treated with dronedarone compared with sotalol had significantly lower rates of CV hospitalization and ventricular arrhythmias, and numerically lower rates of mortality and bradyarrhythmias associated with syncope/pacemaker implant. These findings provide physicians with real-world evidence to support selection of

the most appropriate first-line AAD for rhythm control in patients with AF.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: Current American College of Cardiology/American Heart Association/American College of Clinical Pharmacy/Heart Rhythm Society and European Society of Cardiology AF guidelines underscore the importance of safety first when choosing an AAD for rhythm control in patients with non-permanent AF.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Previous studies have suggested that compared with sotalol, dronedarone may have a lower risk for CV hospitalization, ventricular arrhythmias, and all-cause death.

TRANSLATIONAL OUTLOOK: This meta-analysis found a significantly lower risk of CV hospitalization and ventricular arrhythmias with dronedarone compared with sotalol, providing physicians with comparative evidence when selecting a first-line, guideline-recommended AAD among similarly indicated patients with AF.

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KEY WORDS **antiarrhythmic drugs, atrial fibrillation, dronedarone, meta-analysis, safety, sotalol**

APPENDIX **For a supplemental appendix, please see the online version of this article.**