Outcomes Associated with Dronedarone Use in Patients with Atrial Fibrillation

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The antiarrhythmic drug dronedarone was designed to reduce the extra-cardiac adverse effects associated with amiodarone use in treatment of patients with atrial fibrillation / atrial flutter (AF/AFL). This epidemiological study used a retrospective cohort design to compare risk of cardiovascular-related hospitalizations and death in AF/AFL patients treated with dronedarone versus other antiarrhythmic drugs (AADs). AF/AFL patients with incident dronedarone fills were matched by propensity score (PS) to incident users of other AADs. The primary study outcome was hospitalization for cardiovascular (CV) causes within 24 months after the first study drug fill. A secondary composite outcome comprised hospitalization for CV causes or all-cause mortality during follow-up. In the AF/AFL patient cohort meeting eligibility criteria, 6,964 incident users of dronedarone and 25 607 incident users of other AADs were identified. The PS-matched cohort comprised 6,349 Dronedarone users (91.2% of all eligible) and 12,698 other AAD users. Dronedarone patients had a significantly lower risk of hospitalization for a CV event compared to Other AAD users (hazard ratio = 0.87; 95% confidence interval = 0.79 to 0.96). This was consistent with results for the composite outcome (hazard ratio=0.86; 95% confidence interval = 0.78 to 0.95). In conclusion, AF/AFL patients initiated on dronedarone versus other AADs had significantly lower risk of CV hospitalizations as well as the composite CV hospitalization / death from any cause. **(Am J Cardiol 2020;135:77−83)**

Atrial fibrillation (AF) is the most common cardiac arrhythmia requiring medical care. An estimated 5.3 million United States (US) patients are currently affected by AF, and its incidence is projected to double by 2030.[1−3] While anticoagulation treatment is determined from the CHA_2DS_2-VASc risk score, the choice of a rhythm-control strategy to restore/maintain normal sinus rhythm on top of a ventricular rate-control strategy is dependent on AF/atrial flutter (AFL) type, severity of symptoms and the presence or absence of structural heart disease.[4] Amiodarone is the most commonly used antiarrhythmic drug (AAD); however its safety profile includes long-term thyroid, pulmonary, hepatic and neurologic toxicities.[5] Dronedarone was approved by the US Food and Drug Administration (FDA) in July 2009 to reduce the risk of cardiovascular (CV) hospitalization in patients with paroxysmal or persistent AF/AFL[6] and in Europe for maintenance of sinus rhythm after cardioversion in clinically stable adult patients with paroxysmal or persistent AF.[7] Pharmacologically related to amiodarone, dronedarone was designed to reduce the older drug's extra-cardiac adverse effects.[8] The ATHENA study ("A Trial with Dronedarone to Prevent Hospitalization or Death in Patients with Atrial Fibrillation" [NCT00174785]) found a significant reduction in the primary end point of CV hospitalization/death from any cause in patients randomized to dronedarone versus placebo.[9] While other studies have examined dronedarone's safety and effectiveness,[10−21] the purpose of this study was to compare the risk of CV hospitalization/death following initiation of dronedarone versus other AAD therapy for the treatment of AF/AFL in a "real-world" setting.

Methods

This retrospective cohort study was conducted using the United States Department of Defense Military Health System (DOD) database. The DOD covers almost 10 million active members and their beneficiaries and has been shown to resemble the overall US population with respect to both demographic and health characteristics.[22] The DOD database includes information on each recipient of health care through the DOD and each medical encounter, including physician visits, hospitalizations, laboratories, diagnostic testing, and prescription medications. Variables include patient demographics (age, gender, and race), provider

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information (provider ID, specialty, and facility), International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)[23] diagnostic and procedure codes for inpatient and outpatient encounters, Current Procedural Terminology (CPT)[24] and Healthcare Common Procedure Coding System (HCPCS)[25] codes for any procedures. For each prescription drug dispensed, details include the drug name and National Drug Code, dose, quantity, refills, and prescribing provider identifiers.

The study period covered the 3 years between July 20, 2008 and July 19, 2011, with the first year of data (July 20, 2008 to July 19, 2009) used for ascertainment of patient baseline characteristics, and the latter 2 years for outcome observation. The study was conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practice.[26]

The study cohort was limited to patients with a diagnosis of AF/AFL (ICD-9-CM codes 427.3, 427.31, and 427.32) and treated with an AAD. Patients selected for the analysis had their first prescription fill (Index Fill) of dronedarone, amiodarone, dofetilide, flecainide, propafenone, or sotalol (Index Drug) at any time during the 2-year period from July 20, 2009 through July 19, 2011, and no previous use of their Index Drug in the 12 months preceding the Index Fill (baseline). These were considered incident users for this analysis. Patients with fills of both dronedarone and another AAD on the date of their Index Fill (Index Date) were not eligible for the study, although patients in the Other AAD cohort could be prescribed a second AAD (other than dronedarone) during follow-up. Patients who had an AF/AFL diagnosis within 12 months prior to their Index Date were eligible for the study.

The study cohorts were also limited to patients age 18 or older as of their Index Date, with a minimum 12 months of health plan eligibility before the Index Date, and no history of heart transplant during the baseline.

The primary outcome of interest was hospitalization for selected CV causes (i.e., AF/AFL, ablation, cardioversion, acute coronary syndrome-myocardial infarction, transient ischemic attack, cerebrovascular accident, heart failure, systemic arterial embolism, stable angina, arrhythmia, syncope, cardiovascular surgery, pulmonary embolism, and deep vein thrombosis). The secondary outcome of interest was CV hospitalization or death from any cause, which was the primary end point of the ATHENA trial. All outcomes were defined using ICD-9-CM diagnosis and procedure codes, CPT codes or HCPCS codes.

Follow-up time for the analyses included only that time during which a patient was taking the Index Drug. Patients were censored following the earliest occurrence of (1) discontinuation of the Index Drug, (2) switch to, or augmentation with the other study drug, (3) loss of eligibility for health care in the DOD, (4) death, or (5) end of the study period (i.e., July 19, 2011). Discontinuation was defined as having no subsequent prescription records for the Index Drug starting from the Index Date, plus the days' supply of the last fill, plus 60 days to account for variability in half-lives of the study medications. Although dronedarone has a relatively short half-life of 13 to 19 hours,[6] those of other AADs are longer. The mean half-life of amiodarone, which accounts for more than half of other AADs prescribed to patients in the comparator cohort, is 53 days.[27] Sixty days allowed for coverage of all medications included in the study. Switching was defined as addition of the other study drug during the follow-up period, accompanied by discontinuation of the Index Drug. Augmentation was defined as having concurrent therapy with both dronedarone and another AAD for greater than 30 days during the course of therapy with the Index Drug.

To control for potential confounding and bias due to absence of randomization in this observational study, patients from the Other AAD cohort were matched to the Dronedarone cohort on the basis of a propensity score (PS) designed to predict the probability of membership in the Dronedarone treatment cohort. The PS was calculated from a logistic regression model with membership in the Dronedarone cohort as the dependent variable, and patient baseline characteristics identified from the DOD electronic health records as covariates. The covariates included available demographics (e.g., age, gender), healthcare utilization (e.g., in- and out-patient medical visits), CV diagnoses, procedures, medications and risk factors, and number of different nonstudy medications. The initial set of 48 covariates was reduced to the 37 included in the final model via stepwise elimination. The list of baseline characteristics included in the full and reduced PS models is provided in **Supplemental Table 1**.

The selected matching algorithm required 2 Other AAD patients per Dronedarone patient, matched to a caliper width of 0.01 (i.e., the absolute difference between propensity scores must be ≤ 0.01 for a match). Choice of caliper width (maximum acceptable difference between propensity scores for a match) effects a tradeoff between bias and variance in the matched dataset.[28,29] The selected combination of matches and caliper width was found to optimize the concurrent goals of an analysis dataset containing the largest possible number of patients with a good balance of baseline characteristics. Matching was conducted without replacement (i.e., each comparator patient was matched to only 1 Dronedarone patient). Dronedarone patients for whom 2 acceptable matches could not be found were excluded from the analysis. All analyses were performed on the subset of PS-matched Dronedarone and Other AAD patients.

Baseline characteristics were compared between the 2 therapy cohorts for all eligible patients, and for the PS matched cohorts used in the outcomes analyses. Prevalence rates of each post-Index Date outcome of interest were compared between the PS-matched Dronedarone and Other AAD cohorts, using the Fisher Exact test. Incidence rates per 10,000 person months of exposure were similarly compared, using the log-rank test. Survival analyses utilized Cox Proportional Hazards Regression (CPH) and Kaplan-Meier (K-M) analysis to assess relative differences in outcome-free survival through the follow-up period. Each endpoint was considered an event of independent interest and was tested at the 0.05 alpha level.

All statistical analyses were conducted using SAS version 9.4 (Cary, North Carolina).

Results

A total of 32,571 eligible new *Dronedarone* or *Other AAD* users were identified in the DOD data. With PS

matching, the analytic cohort comprised 6,349 incident *Dronedarone* patients (91.2% of *Dronedarone* patients meeting all screening criteria) and 12,698 patients who were incident users of *Other AADs*. Among the PS-matched *Other AAD* users, 51.5% were prescribed amiodarone (monotherapy for all but 3 patients), 20.4% sotalol, 14.3% flecainide, 11.5% propafenone, and 2.3% dofetilide. Mean duration of follow-up among all PS-matched patients was 6.5 months (SD: 5.3 months); 6.6 months (SD: 5.3 months) among *Dronedarone* users and 6.5 months (SD: 5.3 months) among *Other AAD* users.

Table 1 provides a side-by-side comparison of the baseline demographic and clinical characteristics included in the final PS model for new users in the *Dronedarone* and *Other AAD* cohorts, both before and after PS matching. Using a standardized difference < 5 as an indication of balance on any given covariate, the table shows that while nearly all 37 characteristics included in the reduced PS

Table 1
Dronedarone and other AAD baseline characteristics included in propensity score model, before and after propensity score matching

Baseline characteristics	Before Propensity Score Matching			After Propensity Score Matching		
	Dronedarone (N=6964)	Other AAD (N=25607)	Standardized Difference[a]	Dronedarone (N=6349)	Other AAD (N=12698)	Standardized Difference[a]
Mean age (years) (SD)	71.75 (9.71)	72.36 (10.07)	6.19	71.85 (9.80)	71.83 (10.03)	0.18
Mean Charlson score (SD)	2.10 (2.22)	2.48 (2.49)	15.61	2.15 (2.25)	2.22 (2.40)	3.30
Mean days from start of study to index date (SD)	416.92 (184.36)	351.47 (210.82)	31.85	410.12 (185.64)	405.16 (193.67)	2.60
Male	3859 (55.41%)	15009 (58.62%)	6.49	3541 (55.77%)	7034 (55.39%)	0.76
Mean number of office visits (SD)	10.90 (8.19)	10.01 (7.96)	11.19	10.79 (8.18)	10.67 (8.12)	1.48
Number and percent of cohort with history of condition, procedure, or medication therapy in the 12 months prior to index date:						
Chronic obstructive pulmonary disease	1739 (24.97%)	7170 (28.00%)	6.80	1600 (25.20%)	3221 (25.37%)	0.38
Coronary heart disease	3780 (54.28%)	15771 (61.59%)	14.95	3451 (54.36%)	6899 (54.33%)	0.05
Diabetes mellitus	2245 (32.24%)	9117 (35.60%)	7.07	2050 (32.29%)	4166 (32.81%)	1.11
Heart failure	2070 (29.72%)	10626 (41.50%)	24.26	1994 (31.41%)	4050 (31.89%)	1.05
Non-ischemic cardiomyopathy	830 (11.92%)	4617 (18.03%)	16.41	807 (12.71%)	1625 (12.80%)	0.26
Structural heart disease[b]	2009 (28.85%)	8090 (31.59%)	5.94	1881 (29.63%)	3753 (29.56%)	0.16
TIA, CVA or late effect of cerebrovascular disease	893 (12.82%)	3840 (15.00%)	6.17	830 (13.07%)	1690 (13.31%)	0.70
Valvular heart disease	3005 (43.15%)	11943 (46.64%)	7.00	2742 (43.19%)	5473 (43.10%)	0.17
Cardiac surgery	1329 (19.08%)	8485 (33.14%)	30.87	1305 (20.55%)	2631 (20.72%)	0.41
Major heart surgery	714 (10.25%)	6065 (23.68%)	33.39	709 (11.17%)	1409 (11.10%)	0.23
Pacemaker insertion/evaluation/removal	1076 (15.45%)	4328 (16.90%)	3.90	986 (15.53%)	2000 (15.75%)	0.61
Stent placement	292 (4.19%)	1370 (5.35%)	5.26	274 (4.32%)	560 (4.41%)	0.46
Valve placement	71 (1.02%)	1309 (5.11%)	20.39	71 (1.12%)	116 (0.91%)	2.08
Valve surgery	30 (0.43%)	483 (1.89%)	11.70	30 (0.47%)	49 (0.39%)	1.35
Angiotensin-converting-enzyme inhibitor prescription	2298 (33.00%)	9056 (35.37%)	4.97	2114 (33.30%)	4288 (33.77%)	1.00
Any anticoagulant prescription	3762 (54.02%)	9557 (37.32%)	34.30	3210 (50.56%)	6363 (50.11%)	0.90
Dabigatran prescription	265 (3.81%)	421 (1.64%)	15.08	194 (3.06%)	366 (2.88%)	1.03
Warfarin prescription	3518 (50.52%)	8988 (35.10%)	31.97	3013 (47.46%)	5968 (47.00%)	0.92
Aspirin prescribed by physician	187 (2.69%)	538 (2.10%)	3.96	168 (2.65%)	304 (2.39%)	1.62
Beta blocker prescription	4696 (67.43%)	16124 (62.97%)	9.30	4217 (66.42%)	8441 (66.48%)	0.12
Calcium channel blocker prescription	3029 (43.50%)	9556 (37.32%)	12.70	2674 (42.12%)	5350 (42.13%)	0.03
Statin prescription	4307 (61.85%)	14704 (57.42%)	8.98	3831 (60.34%)	7672 (60.42%)	0.16
Ablation	280 (4.02%)	742 (2.90%)	6.44	242 (3.81%)	460 (3.62%)	1.00
Acute myocardial infarction	817 (11.73%)	5363 (20.94%)	23.60	798 (12.57%)	1584 (12.47%)	0.29
Stable angina pectoris	785 (11.27%)	3382 (13.21%)	5.79	717 (11.29%)	1417 (11.16%)	0.42
Cerebrovascular accident	591 (8.49%)	2587 (10.10%)	5.45	550 (8.66%)	1100 (8.66%)	0.00
Deep vein thrombosis	301 (4.32%)	1511 (5.90%)	6.89	283 (4.46%)	574 (4.52%)	0.30
Hospitalization for bleeding	2503 (35.94%)	10926 (42.67%)	13.69	2337 (36.81%)	4683 (36.88%)	0.15
Syncope	1015 (14.57%)	3776 (14.75%)	0.48	944 (14.87%)	1871 (14.73%)	0.38
Systemic arterial embolism	69 (0.99%)	470 (1.84%)	6.62	69 (1.09%)	139 (1.09%)	0.08
Transient ischemic attack	425 (6.10%)	1567 (6.12%)	0.07	384 (6.05%)	800 (6.30%)	1.04
Hospitalization	4106 (58.96%)	19290 (75.33%)	36.80	3964 (62.44%)	7994 (62.95%)	1.08
Skilled nursing facility stay / visit	208 (2.99%)	1688 (6.59%)	15.43	208 (3.28%)	402 (3.17%)	0.63

[a] Variables with standardized differences < 5 are considered balanced.
[b] History of structural heart disease was identified from ICD-9-CM codes 427, 427.0, 427.1, 427.2 and 427.9.
Abbreviations: AAD=Antiarrhythmic drugs; CVA=Cerebrovascular Accident; TIA=Transient Ischemic Attack

Table 2
Numbers of outcomes, rates per 10,000 person months of follow-up and Hazard Ratios in propensity score-matched AF/AFL patients with incident fills[a] of dronedarone or other antiarrhythmic drugs

Outcomes	Dronedarone (n = 6,349)		Other AAD (n = 12,698)		Hazard ratio (Dronedarone / other AAD)
	n (%)	Event rate[b]	n (%)	Event rate[b]	HR (95% CI)
Cardiovascular hospitalization[c]	586 (9.23%)*	149.48‡	1,315 (10.36%)	173.57	0.87 (0.79−0.96)‖
Cardiovascular hospitalization[c] / death from any cause	598 (9.42%)†	151.32§	1,364 (10.74%)	178.60	0.86 (0.78−0.95)¶

Abbreviations: AAD = Antiarrhythmic drugs; AF/AFL = Atrial fibrillation/Atrial flutter; N = Number of patients.

[a] For this analysis an incident fill was a first prescription fill of dronedarone, amiodarone, dofetilide, flecainide, propafenone or sotalol (Index Drug) at any time during the 2-year period from July 20, 2009 through July 19, 2011 (Index Date), with no prior use of the Index Drug in the 12 months preceding the Index Date.

[b] Event rate per 10,000 person months of follow-up

[c] Any hospitalization with a primary discharge diagnosis considered a cardiovascular outcome, for the purposes of this analysis, between the Index Date and censor date (i.e., atrial fibrillation, ablation, cardioversion, acute coronary syndrome-myocardial infarction, transient ischemic attack, cardiovascular accident, heart failure, systemic arterial embolism, stable angina, arrhythmia, syncope, cardiovascular surgery, pulmonary embolism, or deep vein thrombosis)

* Significantly different from proportion of Other AAD cohort by chi-square test; p = 0.015

† Significantly different from proportion of Other AAD cohort by chi-square test; p = 0.005

‡ Significantly different from Other AAD rate by log-rank test; p = 0.006

§ Significantly different from Other AAD rate by log-rank test; p = 0.002

‖ p = 0.006

¶ p = 0.002

model were unbalanced before matching, all were balanced in the PS-matched analysis dataset.

Patients in the PS-matched *Dronedarone* cohort had significantly lower rates of post-Index Date CV hospitalization (149.5 / 10,000 patient months of follow-up vs 173.6 / 10,000 patient months of follow-up for the *Other AAD* cohort; p = 0.006) (**Table 2**). Among the CV hospitalizations, the most frequently reported were atrial fibrillation, CV surgery, and heart failure. (**Supplemental Table 2**)

The incidence rate for the composite outcome CV hospitalization/death from any cause was also significantly lower in the *Dronedarone* cohort (151.3 / 10,000 months of patient follow-up versus 178.6 / 10,000 months of patient follow-up for the *Other AAD* cohort; p=.002) (**Table 2**).

Hazard ratios comparing risk of the outcomes between the therapy cohorts showed corresponding results (**Table 2**), and Kaplan-Meier analyses graphically mirror the lower risk of these outcomes in the *Dronedarone* cohort through the end of the observation period (**Figure 1**).

Discussion

This analysis is the first, to our knowledge, to assess the relative effectiveness of dronedarone versus other AADs in real-world medical care for the reduction of CV hospitalizations and death in AF/AFL patients. Data were drawn from the large US DOD healthcare database. The study period comprised the first 2 years of dronedarone's approval in the US before label changes in the US and in the EU. Dronedarone was associated with a small but statistically significant reduction in the risk of CV hospitalization and the combined endpoint of CV hospitalization / death from any cause when compared with other AADs, of which 51.5% were amiodarone. This result was similar for both outcomes and is consistent with results of the ATHENA clinical trial.

Potential bias and confounding of results were minimized through use of PS matching, which generated analysis cohorts that were well balanced with respect to baseline demographic and medical characteristics. The average follow-up time after therapy initiation in the PS-matched cohorts was roughly 6.5 months per patient.

More than 16% of *Dronedarone* and 14% of *Other AAD* patients had post-Index Date cardioversion (primarily outpatient). Although this cannot be determined from the data itself, it is possible that some proportion of these patients may have started drug therapy while awaiting cardioversion. (**Supplemental Table 2**) A longer follow-up period might have shown an even wider gap in CV hospitalization rates as cardioversion was achieved for more of the *Dronedarone* cohort. The *Dronedarone* cohort's higher rate of nonhospitalized cardioversion (282.4 / 10,000 months of patient follow-up vs 247.8 / 10,000 months of patient follow-up for the *Other AAD* cohort; p = 0.002) might also reflect its indication for patients awaiting cardioversion. Overall, only 486 (17.4%) of the 2,790 patients with at least 1 post-Index Date nonhospitalized cardioversion event also had a CV hospitalization (14.8% of *Dronedarone* patients and 18.9% of *Other AAD* patients). (**Supplemental Table 2**)

The close balance of baseline characteristics between the PS-matched *Dronedarone* and *Other AAD* analysis cohorts lends confidence to these findings as attributable to differences between the therapies. Still, it is important to note that neither PS matching nor any method other than randomization can eliminate bias from unmeasured confounders. As with any retrospective database analysis, some confounding factors and clinical details were not available and were therefore not part of the PS matching (e.g., the proportions of paroxysmal, persistent, or permanent AF patients, severity of congestive heart failure, and physician preference for treatment regimen). Although the analysis cohorts were closely matched on major established risk factors, remaining unmeasured differences between the PS-matched groups could influence the findings. For example, although not explorable in these data, we hypothesize that

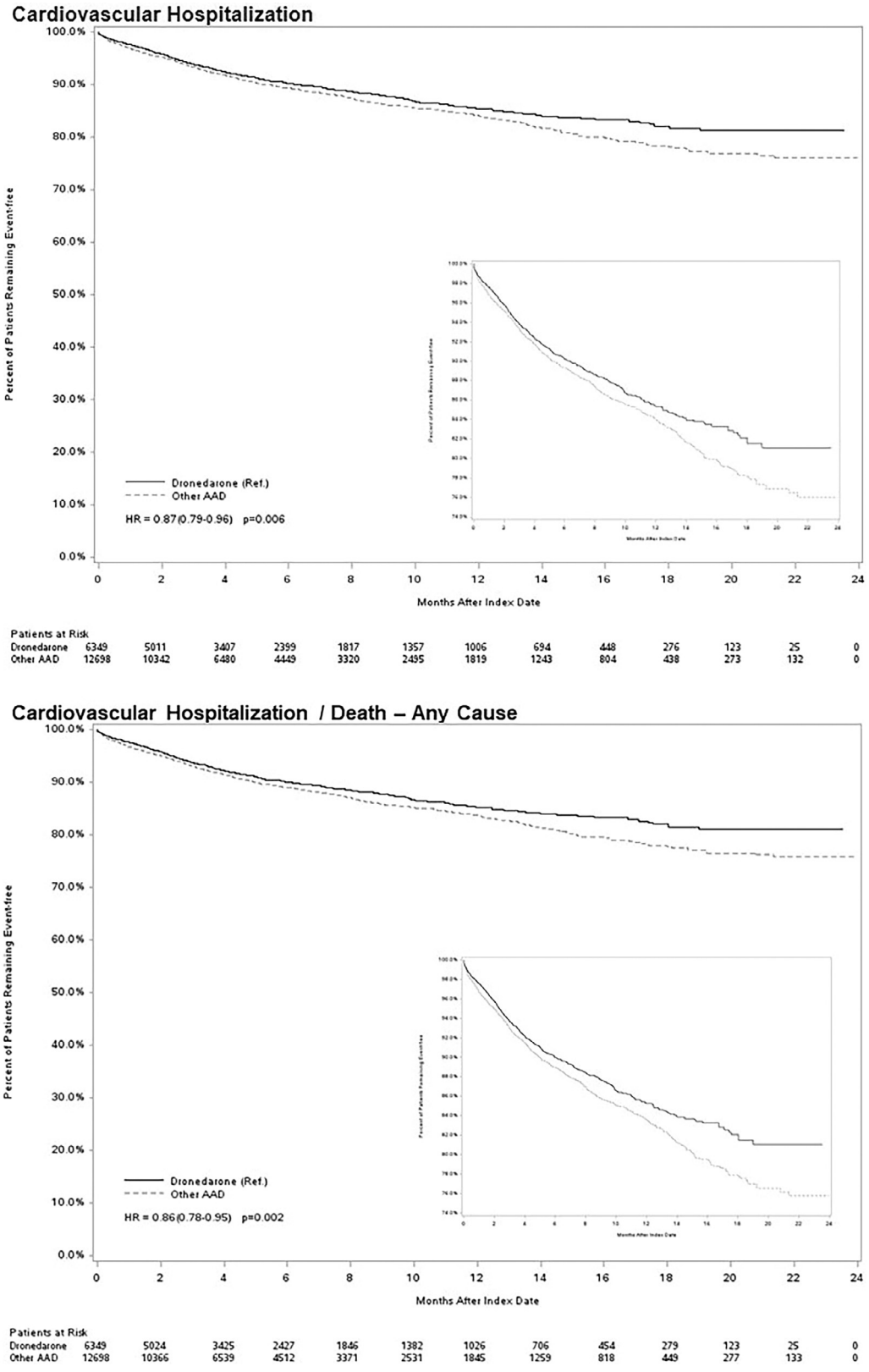

Figure 1. Kaplan-Meier curves comparing Dronedarone versus Other AADs on selected post-index outcomes, PS-matched AF/AFL patients with Incident fills of dronedarone or other AADs.

Cardiovascular Hospitalization. Cardiovascular Hospitalization / Death−Any Cause.

Abbreviations: AAD = antiarrhythmic drugs; HR = Hazard Ratio.

physicians prescribing dronedarone during the first 2 years of approval in the US might have been early adopters of the new therapy as a means of reducing in-patient procedures among AF/AFL patients. The *Dronedarone* cohort's lower risk of hospitalization for arrhythmia (HR = 0.56; p <0.001) might also reflect those clinicians' treatment preferences. Furthermore, there is a potential for interaction among multiple AADs prescribed to patients in the *Other AAD* cohort. (**Supplemental Table 2**)

These findings are generally consistent with and/or reflect knowledge gained from relevant clinical trials. However, differences in research designs caution against drawing direct comparisons. Whereas this real-world comparative analysis used data available from the large DOD database, the clinical trials involved patients who were carefully selected for studies of specific endpoints and involved collection of data for predefined follow-up times. In the case of ATHENA, the comparator group was treated with placebo rather than an alternative antiarrhythmic as in this study. Although 31% of patients in this study had a history of congestive heart failure, our findings similar to ATHENA suggest that clinicians avoided prescribing the drug for contraindicated patients with symptomatic heart failure with recent decompensation requiring hospitalization or NYHA class IV heart failure. Findings of this large US real-world study comparing rates of CV hospitalization between AF patients treated with dronedarone versus other AADs are consistent with evaluations conducted in other countries. Friberg demonstrated a lower risk of ventricular proarrhythmia and mortality in Swedish patients treated with dronedarone compared to sotalol,[21] and Ehrlich, et al. found a lower risk of myocardial infarction and stroke with dronedarone compared to other anti-arrhythmic drugs in an analysis of AF patients treated in German general or cardiology practices.[19]

In conclusion, this real-world comparative analysis shows dronedarone to be an effective alternative to other AADs for reduction of CV hospitalizations and all-cause death in AF/AFL patients. Dronedarone was associated with significantly lower risk of hospitalization for CV events, as well as for the composite outcome CV hospitalization/death from any cause, compared to other AADs in this large group of patients treated for AF/AFL during the drug's first 2 post-approval years.

Further research should include an update of this analysis using additional years of DOD data. In addition to an extended observation period, a longer timeframe might also provide sufficient numbers of outcomes to support more detailed sub-analyses.

Replicating the analysis with healthcare data from countries other than the US should also be considered. Findings from DOD data can be considered representative of the overall US population, but their generalizability to the global population is uncertain. In addition, variations in patient care and hospitalization practices by country might influence results.

Conflicts of Interest

Mr. Goehring, Ms. Tave, Dr. Jones, and Dr. Bohn declare that they have no conflicts of interest. Ms. Bozzi is an employee of Sanofi. Dr. Tamayo is a retired member of the US military; this work was prepared as part of her official duties. Dr. Naccarelli is a consultant for Janssen, Sanofi, Acesion, Omeicos, Milestone, and Correvio. Mr. Sicignano is an employee of Health ResearchTx.

Statement of Human Rights

For this type of study formal consent is not required.

Disclaimer

Research data derived from an approved Naval Medical Center, Portsmouth, Virginia IRB, protocol; number NMCP.2014.0044. The views expressed in this manuscript reflect the results of research conducted by the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government. Copyright Notice: CAPT Sally Tamayo, MC, USN, (Ret.) was a military service member. This work was prepared as part of her official duties. Title 17 U.S.C. 105 provides that "Copyright protection under this title is not available for any work of the United States Government." Title 17 U.S.C. 101 defines a United States Government work as a work prepared by a military service member or employee of the United States Government as part of that person's official duties.

Authors contribution

Goehring EL Jr: Conceptualization, Methodology, Project administration, Writing−Review & Editing.

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Pezzullo J: Conceptualization, Methodology.

Tave AK: Formal analysis; Writing−Original Draft.

Jones JK: Conceptualization, Methodology, Supervision, Writing−Review & Editing.

Bozzi S: Conceptualization, Funding acquisition, Methodology, Project administration, Writing−Review & Editing.

Tamayo SG: Conceptualization, Methodology, Supervision, Writing−Review & Editing.

Naccarelli GV: Conceptualization, Methodology, Writing−Review & Editing.

Sicignano N: Methodology, Writing−Review & Editing.

Disclosure

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

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Supplementary materials

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