JAFIB
Original Research
Journal of Atrial Fibrillation

www. jafib.com

Risk of Cardiovascular Events, Stroke, Congestive Heart Failure, Interstitial Lung Disease, and Acute Liver Injury: Dronedarone versus Amiodarone and Other Antiarrhythmics

Shujun Gao, MD, MPH, PhD[1], Wanju Dai, MD, DrPH[2], Ling Zhang, MS[2], Juhaeri Juhaeri[2], MS, PhD, Yunxun Wang[2], MS, Patrick Caubel, MD, PhD, MBA[2]

[1]Clinical Safety and Pharmacovigilance, Daiichi Sankyo, Edison, NJ 08837, USA. [2]Global Pharmacovigilance and Epidemiology, Sanofi, Bridgewater, 08807, USA

Abstract

No published studies have evaluated the risks of cardiovascular (CV) events, stroke, congestive heart failure (CHF), interstitial lung disease (ILD), and severe acute liver injury (ALI) related to antiarrhythmics treatment in real-world clinical practice setting. We examined the relationship between the above events and the selected antiarrhythmics in the real-world setting in the US.. Using a retrospective cohort design, the hazard ratios of the outcome events were analyzed from 10,455 adult patients with a diagnosis of atrial fibrillation/atrial flutter and a new treatment with dronedarone (comparison drug), amiodarone, sotalol, flecainide, or propafenone between 07/20/2009 and 12/31/2010 from the Clinformatics Data MartTM database. The patients were followed until: 1) switch to another antiarrhythmic drug, 2) occurrence of the outcome event, 3) end of enrollment, or 4) end of the study period, whichever occurred first. No significant differences were observed in the hazard ratios of the outcome events between dronedarone, amiodarone, and the other antiarrhythmics, except that amiodarone was associated with a higher risk of CV events (adjusted HR = 1.7, 95%CI: 1.1-2.4) and stroke (adjusted HR = 2.0, 95%CI: 1.3-3.2), compared to dronedarone, especially amongst patients without a CHF history (adjusted HR = 2.4, 95%CI: 1.4-3.8 and 2.2, 95%CI: 1.2-3.9). A higher risk of CHF was also associated with amiodarone in patients without history of CHF at baseline (adjusted HR = 2.7, 95%CI: 2.0-3.6). In this real-world investigation, no difference in risk was observed between dronedarone, sotalol, flecainide and propafenone initiators for CV events, stroke, CHF, ILD, and ALI. Amiodarone was associated with higher risks of CV events, stroke, and CHF than dronedarone in patients without a CHF history, indicating dronedarone could be an alternative therapy option with lower risk of CV events than amiodarone for the above patients.

Introduction

Dronedarone is an antiarrhythmic drug indicated in the U.S for the treatment of patients with non permanent atrial fibrillation (AF) to reduce the risk of hospitalization for AF. Based on comprehensive clinical trial data, particularly ATHENA, a placebo-controlled, double-blind, parallel arm trial in 4,628 patients with non-permanent AF, dronedarone demonstrated favorable benefit risk profile in patients with non permanent AF or AFL (or with history of such events).

More recently, significant increased risks of cardiovascular events including cardiovascular death, stroke, and hospitalization for heart failure were observed in the dronedarone-treated arm in the PALLAS trial in patients with permanent AF.[3] In addition, post-marketing pharmacovigilance data of spontaneous reports have shown some potential safety signals related to severe acute liver injury (ALI) and interstitial lung disease (ILD),[4] even though the results from clinical trials including ATHENA showed dronedarone was not associated with an increased risk of amiodarone-like adverse events such as thyroid disorders, interstitial lung disease, neuropathy or hepatic disorders .[2] The US labeling for dronedarone has been revised, accordingly, based on these post-marketing reports. In order to examine these associations in the real-world setting, where dronedarone is approved for non-permanent AF/AFL, we conducted this retrospective cohort study.

Key Words:
Dronedarone, Relative Risk, Claims Database, Cohort Study

Disclosures:
The authors are current employees or former (Gao and Dai) of sanofi-aventis, the manufacturer of dronedarone and amiodarone..

Corresponding Author:
Shujun Gao, MD, MPH, PhD
Clinical Safety and Pharmacovigilance
Daiichi Sankyo, Inc.
399 Thornall Street
Edison, NJ 08837• USA

Material and Methods

Study Population

We conducted this study using the Clinformatics Data MartTM,[1] a US private insurance claims database. This database represents a broad US population in terms of age, gender and region distributions, although a lower proportion of patients aged 65+ years was covered compared to the general US population (6% vs. 12%).[1]

Table 1: Characteristics of the study cohort during baseline period for the cardiovascular events

Characteristics	Study cohort	Dronedarone	Amiodarone	Sotalol	Flecainide	Propafenone
N	Included	1,727	2,782	1,366	1,502	1,146
	Excluded	1,342	4,077	3,767	3,318	2,424
Age years, mean (SD)	Included	61.1 (10.7)	64.0 (11.8)	61.3 (11.6)	56.3 (11.3)	57.3 (11.7)
	Excluded	60.4 (10.5)	65.8 (11.9)	62.6 (11.7)	58.9 (11.1)	60.1 (11.1)
Gender (female)	Included	521 (30.2%)	769 (27.6%)	426 (31.2%)	529 (35.2%)	391 (34.1%)
	Excluded	396 (29.5%)	1121 (27.5%)	1210 (32.1%)	1232 (37.1%)	900 (37.1%)
Number of AF/AFL Dx	Included	6.9 (5.7)	6.4 (5.9)	6.2 (5.3)	5.1 (5.1)	5.2 (5.2)
	Excluded	8.7 (6.9)	6.5 (6.9)	5.2 (5.6)	4.4 (5.1)	4.4 (4.8)
CHF	Included	325 (18.8%)	1,168 (42.0%)	255 (18.7%)	68 (4.5%)	93 (8.1%)
	Excluded	270 (20.1%)	1,310 (32.1%)	543 (14.4%)	151 (4.6%)	138 (5.7%)
Diabetes	Included	392 (22.7%)	883 (31.7%)	326 (23.9%)	199 (13.2%)	173 (15.1%)
	Excluded	286 (21.3%)	1130 (27.7%)	929 (24.7%)	443 (13.4%)	416 (17.2%)
Hypertension	Included	1,232 (71.3%)	2,116 (76.1%)	977 (71.5%)	814 (54.2%)	694 (60.6%)
	Excluded	924 (68.9%)	2,960 (72.6%)	2,431 (64.5%)	1,783 (53.7%)	1,404 (57.9%)
Dyslipidemia	Included	490 (28.4%)	837 (30.1%)	364 (26.6%)	263 (17.5%)	245 (21.4%)
	Excluded	411 (30.6%)	1,444 (35.4%)	1,299 (34.5%)	815 (24.6%)	656 (27.1%)
Ventricular arrhythmia	Included	333 (19.3%)	687 (24.7%)	316 (23.1%)	239 (15.9%)	211 (18.4%)
	Excluded	317 (23.6%)	920 (22.6%)	640 (17.0%)	369 (11.1%)	286 (11.8%)
Hx of amiodarone	Included	0	0	0	0	0
	Excluded	405 (30.2%)	3,504 (85.9%)	129 (3.4%)	93 (2.8%)	54 (2.2%)
Hx of dronedarone	Included	0	0	0	0	0
	Excluded	223 (16.6%)	216 (5.3%)	79 (2.1%)	97 (2.9%)	74 (3.1%)
Hx of flecainide	Included	0	0	0	0	0
	Excluded	219 (16.3%)	140 (3.4%)	111 (2.9%)	2981 (89.8%)	96 (4%)
Hx of propafenon	Included	0	0	0	0	0
	Excluded	229 (17.1%)	142 (3.5%)	112 (3%)	140 (4.2%)	2193 (90.5%)
Hx of sotalol	Included	0	0	0	0	0
	Excluded	329 (24.5%)	263 (6.5%)	3455 (91.7%)	140 (4.2%)	76 (3.1%)
Hx of other antiarrythmics	Included	0	0	0	0	0
	Excluded	70 (5.2%)	58 (1.4%)	26 (0.7%)	18 (0.5%)	12 (0.5%)

Excluded patients were the ones with former use of antiarrhythmic drugs but did not have any CV events during baseline period.

The study population included patients aged 18 years and older with a prescription of antiarrhythmics dispensed between July 20, 2009 (the dronedarone launch date in the US) and December 31, 2010 and a diagnosis of AF/AFL during 6-month baseline period before the prescription. Only new antiarrhythmic users were included, which were defined as no use of quinidine, procainamide, disopyramide, flecainide, propafenone, amiodarone, dofetilide, sotalol, or dronedarone in the six-month period prior to the cohort entry date.

Cohort entry date was defined as the date of the first prescription of the selected antiarrhythmics dispensed after July 20, 2009. Patients were excluded from the study cohort if they had: 1) less than six-month enrollment period before the cohort entry date; 2) a diagnosis of the specific outcome event of interest during the 6-month baseline period; or 3) use of quinidine, procainamide, disopyramide, flecainide, propafenone, amiodarone, dofetilide, sotalol, or dronedarone during the 6 month baseline period.

Exposure Measurement

Exposure was defined as the initial episode of antiarrhythmic therapy of the following antiarrhythmics: 1) dronedarone, 2) amiodarone, 3) sotalol, 4), flecainide, or 5) propafenone. Other antiarrhythmics were seldomly dispensed, so were not included in the study. The exposure episode began accumulating on the first dispensing date of the first antiarrhythmic prescription during the study period and continued throughout the continuous treatment duration of the same antiarrhythmic drug. Treatment duration was defined as a continuous period during which a patient was on the designated antiarrhythmic (i.e. drug dispensing date plus days supplied) plus a 30 day grace period (to account for potential non-compliance or missing doses). The treatment episode ended when one of the following conditions occurred: 1) switch to a prescription of another antiarrhythmic drug, 2) occurrence of the outcome event, 3) end of enrollment, or 4) end of the study period, whichever occurred first. In order to minimize any potential prescription or indication biases related to physicians' prescription preferences and/or patients' underlying conditions, only the first episode, i.e. the initial antiarrhythmic therapy was counted in the analyses for patients with multiple treatment episodes on the same exposed drug.

Outcome(S) of Interest

The International Classification of Diseases version 9 (ICD-9)

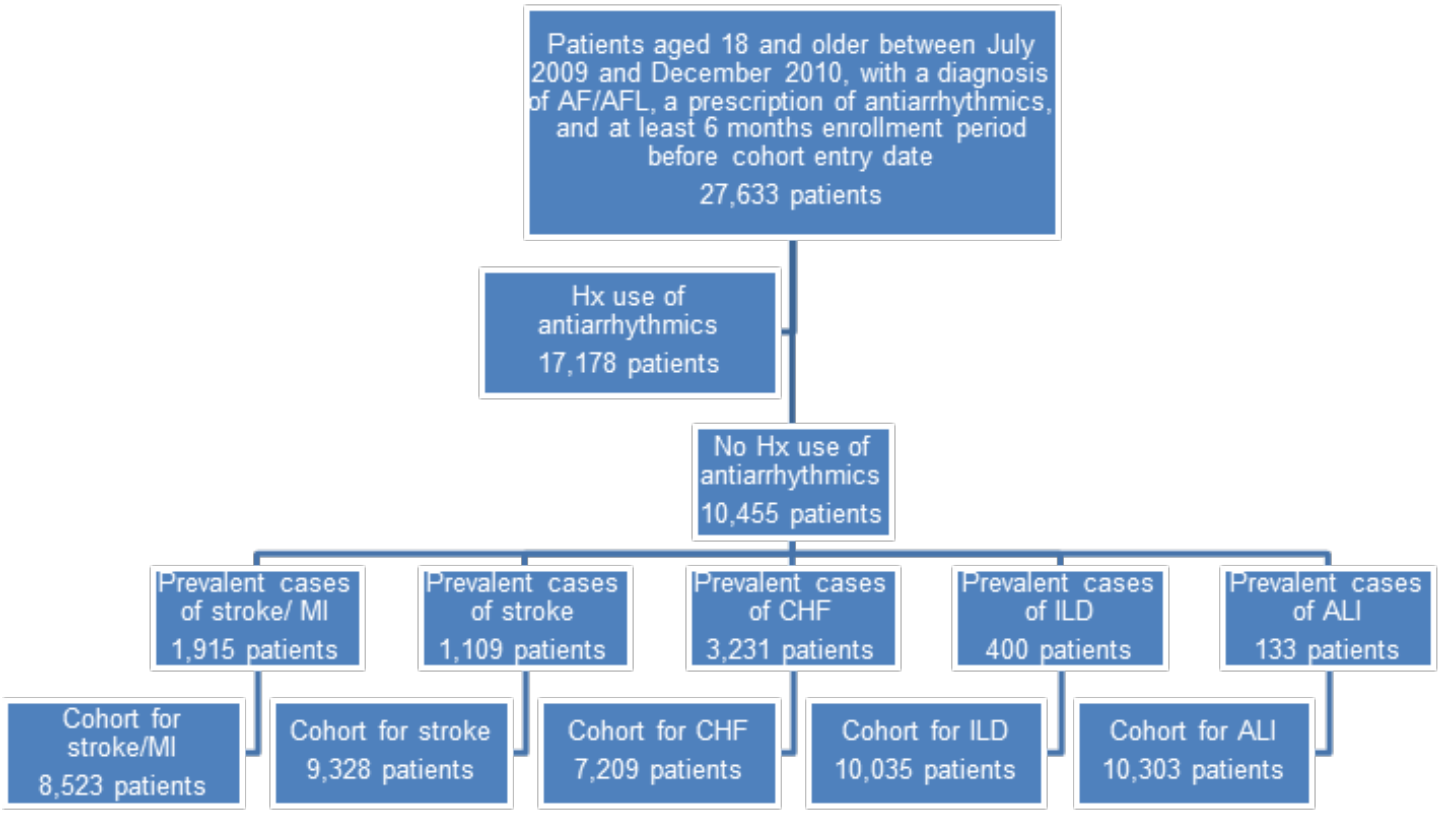

Figure 1: Flow chart of inclusion and exclusion process

codes and Current Procedural Terminology (CPT) code were used to identified outcomes of interest, including cardiovascular events (CV events: 410.x, 433.x1, 435.x, 436, 437.1x, 437.9x, and 438.x), ischemic stroke (433.x1, 436, 437.1x, 437.9x, and 438.x) including transient cerebral ischemia (TIA, 435.x), congestive heart failure (CHF, 428.x, 398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, and 404.93), ILD (515, 516.3, 516.8, 516.9, and 495.9), and ALI (570.x, 572.2, 573.3, CPT codes 47136, 47140, 47141, 47142, and 00796). These codes were selected as they had been validated in other studies using medical insurance claims databases with good specificity (0.97~0.995 for heart failure, stroke/TIA, AMI, liver disease) and/or positive predictive values (0.96~0.97), although their sensitivities were relatively low (0.38 to 0.77) .[5-8] The ICD-9 codes of ILD were selected based on their previous use in studies, and their validity has not been reported.[11]

Statistical Analysis

Cox proportional hazards regression modeling was used to estimate hazard ratio (HR) for each outcome event of interest. The dronedarone initiators served as the reference group. Covariates included age, gender, cohort entry year, number of AF/AFL diagnosis, and history of certain conditions during the baseline period, including CHF, AMI, stroke, diabetes, hypertension, dyslipidemia, and ventricular arrhythmia when they were not outcomes. The history of the health conditions above was defined by at least one diagnosis claim during the baseline period, with the exception of dyslipidemia, which was defined by at least one prescription of "antihyperlipidemics" based on the National Drug Code (NDC) during the baseline period.

Considering that background confounding by indication is a common problem in pharmacoepidemiology,[12] and that the traditional covariate adjustment described above may not fully mitigate the

Table 2: Incidence rates (per 1,000 person-years) and hazard ratio of cardiovascular events

	Dronedarone	Amiodarone	Sotalol	Flecainide	Propafenone
# cases	39	117	38	24	20
Mean treatment duration, month (SD)	4.0 (3.6)	3.6 (3.1)	5.3 (4.4)	4.5 (4.2)	4.1 (4.1)
Incidence rate (95%CI)	68.6 (47.1-90.1)	142.9 (117.0-168.7)	63.8 (43.5-84.1)	43.5 (26.1-61.0)	51.5 (28.9-74.1)
Crude HR (95%CI)	Reference	2.3 (1.8-2.9)	0.8 (0.6-1.2)	0.5 (0.3-0.8)	0.6 (0.4-1.0)
Adjusted HR (95%CI)*	Reference	1.7 (1.1-2.4)	1.0 (0.7-1.6)	0.9 (0.5-1.5)	0.9 (0.5-1.6)

Proportional hazard model, adjusted for age, gender, cohort entry year, number of AF/AFL diagnosis, congestive heart failure, MI, stroke, diabetes, hypertension, dyslipidemia, and ventricular arrhythmia during baseline period

Table 3: Incidence rates (per 1,000 person-years) and hazard ratio of stroke

	Dronedarone	Amiodarone	Sotalol	Flecainide	Propafenone
# cases	24	97	31	20	18
Mean treatment duration, month (SD)	4.0 (3.6)	3.6 (3.1)	5.3 (4.3)	4.5 (4.2)	4.2 (4.1)
Incidence rate (95%CI)	39.5 (23.7-55.3)	98.5 (78.9-118.2)	48.5 (31.4-65.6)	35.8 (20.1-51.5)	45.2 (24.3-66.1)
Crude HR (95%CI)	Reference	2.4 (1.5-3.8)	1.3 (0.8-2.2)	0.9 (0.5-1.7)	1.1 (0.6-2.1)
Adjusted HR (95%CI)*	Reference	2.0 (1.3-3.2)	1.3 (0.7-2.2)	1.2 (0.6-2.2)	1.4 (0.7-2.5)

Proportional hazard model, adjusted for age, gender, cohort entry year, number of AF/AFL diagnosis, congestive heart failure, MI, stroke, diabetes, hypertension, dyslipidemia, and ventricular arrhythmia during baseline period

confounding biases, we did sensitivity analyses using a propensity score matching (PSM) technique.[12,13] The propensity scores were estimated as the probability of new use of an antiarrhythmic drug for the study participants based on their claims over the study period preceding their index dates, using unconditional logistic regression model for each paired comparison (e.g. amiodarone vs. dronedarone) with all selected covariates. Each eligible dronedarone patient was matched to a non-dronedarone patient on 0.01 caliper of propensity. Cox regression was then used to estimate the HR in the PSM cohort for each outcome event.

In addition, we did the following sensitivity analyses: Cox regression analyses stratified by baseline heart failure history (ICD-9 codes of 428.x, 398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, and 404.93), baseline ventricular arrhythmia (ICD-9 codes of 427.1 427.4, 427.5, 427.9 and 798), and left ventricular dysfunction status at baseline separately to minimize potential residual confounding bias. Left ventricular dysfunction was defined as >1 dispensing for digoxin during 180 days before or 30 days after a HF/MI hospitalization and no inpatient diagnosis for atrial fibrillation or flutter during the hospitalization based on a validated algorithm with good specificity (98%) and PPV in literature (94). [14] We also did a Cox regression with the former use of antiarrhythmics as a covariate among patients who were excluded from the primary analyses to investigate the generalizability of the findings.

The Institutional Review Board Approval

An institutional review board (IRB) approval was not necessary[15] per the standards of the Health Insurance Portability and Accountability Act (HIPPA) because it was based on a preexisting, de-identified patient data.

Results

Characteristics of the Traditional Study Cohorts

From the Clinformatics Data Mart database, we identified a total of 27,633 patients aged 18 and older between July 2009 and December 2010, who had at least one diagnosis of AF/AFL and had at least one prescription of antiarrhythmics dispensed during the study period (see Figure 1). We then excluded 17,178 patients who had antiarrhythmics dispensed during the baseline period to ensure only new antiarrhythmic users were included in the study cohort. In order to examine incidence rate and risk, we further excluded patients with the outcome events during the baseline period, leaving a total of 8,523 patients for the analysis for CV events, 9,328 patients for stroke, 7,209 patients for CHF, 10,035 patients for ILD, and 10,303 patients for ALI.

Table 1 shows the baseline characteristics of the 8,523 patients included in the analyses and the 17,178 patients excluded due to the dispense of antiarrhythmicss during the baseline period for CV outcomes by drug exposure groups. These characteristics were similar in the cohorts for the other outcome events (data not shown). In the study cohort for CV events, there were a total of 1,727 patients on dronedarone, 2,782 patients on amiodarone, 1,366 on sotalol, 1,502 patients on flecainide, and 1,146 on propafenone. Patients treated with class III antiarrhythmics, i.e. dronedarone, amiodarone, and sotalol, tended to have a greater proportion of cardiovascular co-morbidities including diabetes, hypertension, dyslipidemia, and ventricular arrhythmia during the baseline period than those treated with class I antiarrhythmics, i.e. flecainide, and propafenone. In addition, patients treated with amiodarone had a greater chance of having a history of CHF than the other two class III antiarrhythmics (42% for amiodarone vs 18.8% for dronedarone and sotalol). The Class I antiarrhythmics were dispensed to patients who were least likely to have a history of CHF (less than 10%).

One major difference in the characteristics of excluded patients compared to the included patients was that in amiodarone users CHF history was more common in the included patients than in the excluded patients (42.0% vs. 32.1%). In both the included and the excluded patients though, amiodarone was dispensed more often to patients with CHF history than the other drugs (e.g. 18.8% in the included dronedarone patients and 20.1% in the excluded dronedarone patients respectively), indicating that physicians preferred to prescribe amiodarone for these patients more than dronedarone and other drugs. The prescription preferences of amiodarone vs. dronedarone were consistent with the fact that dronedarone was the second line drug for patients and contraindicated for use in patients with worsening or unstable heart failure.

Incidence and Hazard Ratio of Cardiovascular Events

Table 2 shows incidence rates (per 1,000 person-years) and HRs of CV events by drug exposure group. The crude incidence rate of CV events in the dronedarone initiators was 68.6 (95%CI: 47.1-90.1) cases per 1,000 person-years, which was statistically significantly lower than that observed in the amiodarone initiators (142.9, 95%CI: 117.0-168.7), but similar to that observed in the other antiarrhythmic groups (63.8, 95%CI: 43.5-84.1 for sotalol; 43.5, 95%CI: 26.1-61.0 for flecainide; 51.5, 95%CI: 28.9-74.1 for propafenone). After

Table 4: Incidence rates (per 1,000 person-years) and hazard ratio of CHF

	Dronedarone	Amiodarone	Sotalol	Flecainide	Propafenone
# cases	57	200	64	40	31
Mean treatment duration, month (SD)	3.9 (3.5)	3.1 (2.9)	5.1 (4.3)	4.5 (4.3)	4.0 (4.0)
Incidence rate (95%CI)	120.9 (89.5-152.2)	405.1 (349.0-461.3)	124.3 (93.8-154.7)	72.5 (50.1-95.0)	84.4 (54.7-114.1)
Crude HR (95%CI)	Reference	3.0 (2.2-4.0)	1.1 (0.8-1.6)	0.7 (0.5-1.1)	0.6 (0.4-1.0)
Adjusted HR (95%CI)*	Reference	2.7 (2.0-3.6)	1.1 (0.8-1.6)	0.8 (0.5-1.1)	0.8 (0.5-1.2)

* Proportional hazard model, adjusted for age, gender, cohort entry year, number of AF/AFL diagnosis, congestive heart failure, MI, stroke, diabetes, hypertension, dyslipidemia, and ventricular arrhythmia during baseline period

Table 5: Incidence rates (per 1,000 person-years) and hazard ratio of ILD

	Dronedarone	Amiodarone	Sotalol	Flecainide	Propafenone
# cases	14	34	15	5	5
Mean treatment duration, month (SD)	4.0 (3.6)	3.7 (3.2)	5.3 (4.3)	4.5 (4.2)	4.2 (4.1)
Incidence rate (95%CI)	21.9 (10.5-33.4)	30.4 (20.2-40.6)	21.6 (10.7-32.5)	8.4 (1.0-15.8)	11.9 (1.5-22.3)
Crude HR (95%CI)	Reference	1.3 (0.7-2.4)	1.1 (0.5-2.2)	0.4 (0.1-1.1)	0.6 (0.2-1.5)
Adjusted HR (95%CI)*	Reference	1.0 (0.5-2.0)	1.1 (0.5-2.2)	0.5 (0.2-1.5)	0.7 (0.2-1.8)

Proportional hazard model, adjusted for age, gender, cohort entry year, number of AF/AFL diagnosis, congestive heart failure, MI, stroke, diabetes, hypertension, dyslipidemia, and ventricular arrhythmia during baseline period

adjustment for covariates, the risk of CV events remained higher in the amiodarone initiators (adjusted HR= 1.7, 95%CI: 1.1-2.4) than that observed in the dronedarone initiators, and comparable between dronedarone and the initiators of other antiarrhythmics.

Incidence and Hazard Ratio of Stroke

Table 3 shows incidence rates (per 1,000 person-years) and hazard ratios of stroke by drug exposure group. The crude incidence rate of stroke in the dronedarone initiators was 39.5 (95%CI: 23.7-55.3) cases per 1,000 person-years, which was not statistically different from that observed in the other antiarrhythmic initiators (48.5, 95%CI: 31.4-65.6 for sotalol; 35.8, 95%CI: 20.1-51.5 for flecainide; 45.2, 95%CI: 24.3-66.1 for propafenone). In contrast, a significantly higher incidence rate of stroke was observed in the amiodarone compared to the dronedarone initiators (98.5, 95%CI: 78.9-118.2). These findings were maintained after adjustment for covariates with a higher risk of stroke only for amiodarone compared with dronedarone (adjusted HR= 2.0, 95%CI: 1.3-3.2).

Incidence and Hazard Ratio of CHF

Table 4 shows incidence rates (per 1,000 person-years) and hazard ratios of CHF by drug exposure group. The crude incidence rate of CHF in the dronedarone initiators was 120.9 (95%CI: 89.5-152.2) cases per 1,000 person-years, which was significantly lower than that observed in amiodarone initiators (405.1, 95%CI: 349.0-461.3), and not statistically different from that observed in the other antiarrhythmic initiators (124.3, 95%CI: 93.8-154.7 for sotalol; 72.5, 95%CI: 50.1-95.0 for flecainide; and 84.4, 95%CI: 54.7-114.1) for propafenone). After adjustment for covariates, the risk of CHF remained higher in the amiodarone (adjusted HR= 2.7, 95%CI: 2.0-3.6) than in the dronedarone initiators, but not different between the dronedarone and the initiators of other antiarrhythmics.

Incidence and Hazard Ratio of ILD

Table 5 shows incidence rates (per 1,000 person-years) and hazard ratios of ILD by drug exposure group. The crude incidence rate of ILD in the dronedarone initiators was 21.9 (95%CI: 10.5-33.4) cases per 1,000 person-years, which was not statistically significantly different from that observed in any of the drug groups, including amiodarone (30.4, 95%CI: 20.2-40.6), sotalol (21.6, 95%CI: 10.7-32.5), flecainide (8.4, 95%CI: 1.0-15.8), and propafenone (11.9, 95%CI: 1.5-22.3). After adjustment for covariates, the risks of ILD were not significantly different between dronedarone and any of the antiarrhythmic groups.

Table 6: Incidence rates (per 1,000 person-years) and hazard ratio of ALI

	Dronedarone	Amiodarone	Sotalol	Flecainide	Propafenone
# cases	5	22	1	3	6
Mean treatment duration, month (SD)	4.0 (3.6)	3.7 (3.2)	5.4 (4.4)	4.6 (4.2)	4.2 (4.1)
Incidence rate (95%CI)	7.6 (0.9-14.2)	18.9 (11.0-26.8)	1.4 (0.0-4.1)	5.0 (0.0-10.7)	14.0 (2.8-25.1)
Crude HR (95%CI)	Reference	2.4 (0.9-6.4)	0.2 (0.0-1.7)	0.7 (0.2-2.9)	1.9 (0.6-6.1)
Adjusted HR (95%CI)	Reference	2.2 (0.8-6.2)	0.2 (0.0-2.0)	0.9 (0.2-3.7)	2.3 (0.7-7.7)

Proportional hazard model, adjusted for age, gender, cohort entry year, number of AF/AFL diagnosis, congestive heart failure, MI, stroke, diabetes, hypertension, dyslipidemia, and ventricular arrhythmia during baseline period

Incidence and Hazard Ratio of ALI

Table 6 shows incidence rates (per 1,000 person-years) and hazard ratios of ALI by drug exposure group. The overall crude incidence rate in the dronedarone initiators was 7.6 (95%CI: 0.9-14.2) cases per 1,000 person-years, which was not statistically significantly than that observed with amiodarone (18.9, 95%CI: 11.0-26.8),. sotalol (1.4, 95%CI: 0.0-4.1), flecainide (5.0, 95%CI: 0.0-10.7), and propafenone (14.0, 95%CI: 2.8-25.1). It should be noted that none of these ALI cases resulted in a hospitalization as a primary diagnosis. After adjustment for covariates, none of the risks of ALI associated with these antiarrhythmics were statistically significantly different compared to dronedarone.

Hazard Ratios by History of CHF

History of CHF at baseline was unbalanced among the 5 drug groups. In order to better evaluate the effect of CHF history on the study outcomes, we stratified the analyses by history of CHF. Table 7 shows the hazard ratios of CV events, stroke, ILD, and ALI by CHF history at baseline. Among patients with a history of CHF, none of the adjusted HRs of the outcome events was found to be statistically significantly different when any of the antiarrhythmic drug groups was compared with dronedarone. However, it should be noted that the numbers of patients with a history of CHF were small for many of the drug groups. In contrast, among patients without a history of CHF, a significantly higher risk of CV events (adjusted HR= 2.4, 95%CI: 1.4-3.8) and stroke (adjusted HR= 2.2, 95%CI: 1.2-3.9) were found in the amiodarone than in the dronedarone initiators, but not in the initiators of other antiarrhythmics. No statistically significant difference of either ILD or ALI was observed for any of the antiarrhythmic groups.

Hazard Ratios by History of Ventricular Arrhythmia

Table 8 shows the hazard ratios of CV events, stroke, ILD, ALI, and CHF by history of ventricular arrhythmia. Among patients with a history of ventricular arrhythmia, no difference in the risk of outcome events were observed after adjustment for covariates, except for the outcome CHF of which a higher risk was associated with amiodarone compared to dronedarone (adjusted HR=6.6, 95%CI: 2.5-17.3). Among patients without a history of ventricular arrhythmia, a significantly higher risk of CV events (adjusted HR= 1.9, 95%CI: 1.2-3.0), stroke (adjusted HR= 2.5, 95%CI: 1.4-4.4), and CHF (adjusted HR=2.3, 95%CI: 1.7-3.2) were found in the

Table 7: Adjusted hazard ratios of CV events, stroke, ILD and ALI by history of CHF (reference group: dronedarone)

	Amiodarone	Sotalol	Flecainide	Propafenone
Patients with history of CHF				
CV events	0.9 (0.5-1.6)	0.5 (0.2-1.1)	0.9 (0.3-3.3)	0.7 (0.2-2.3)
Stroke	1.7 (0.8-3.8)	1.1 (0.4-3.1)	1.4 (0.3-7.0)	1.5 (0.4-5.8)
ILD	1.0 (0.4-2.6)	0.8 (0.2-3.2)	1.7 (0.3-8.8)	No cases
ALI	3.6 (0.5-28.1)	No cases	No cases	3.8 (0.2-61.6)
Patients without history of CHF				
CV events	2.4 (1.4-3.8)	1.4 (0.8-2.4)	1 (0.5-1.8)	1.1 (0.6-2.2)
Stroke	2.2 (1.2-3.9)	1.4 (0.7-2.6)	1.2 (0.6-2.3)	1.4 (0.7-2.7)
ILD	1.1 (0.4-2.5)	1.2 (0.5-2.9)	0.4 (0.1-1.4)	0.9 (0.3-2.6)
ALI	1.8 (0.5-6.2)	0.3 (0.0-2.7)	0.9 (0.2-4.1)	2.2 (0.6-8.4)

Proportional hazard model, adjusted for age, gender, cohort entry year, number of AF/AFL diagnosis, MI, stroke, diabetes, hypertension, dyslipidemia, and ventricular arrhythmia during baseline period

amiodarone than in the dronedarone initiators. No statistically significant difference of either ILD or ALI was observed for any of the antiarrhythmics initiators.

Hazard Ratios by History of Left Ventricular Dysfunction

Table 9 shows the hazard ratios of CV events, stroke, ILD, ALI, and CHF by history of left ventricular dysfunction. Among patients with ventricular dysfunction at baseline, the risk CV events tended to be higher in amiodarone than in dronedarone initiators with a wide confidence interval (adjusted HR = 2.8, 95%CI: 0.3-23.9). For the other outcome events, due to a very limited number of patients with left ventricular dysfunction (only around 250 patients at the maximum of all exposure drug cohorts), the estimates of HR were unavailable as no cases of outcome event were observed in one drug exposure group or another. Among patients without a history of left ventricular dysfunction, the risk of CV events (adjusted HR= 1.6, 95%CI: 1.1-2.3), stroke (adjusted HR= 1.9, 95%CI: 1.2-3.0), and CHF (adjusted HR=2.7, 95%CI: 2.0-3.7) remained higher in the amiodarone than in the dronedarone initiators.

Matahced Propensity Score Analysis

Table 10 displays the characteristics of the PSM cohort before and after matching for cardiovascular events. Before matching, there were significant differences in distribution of the predefined covariates between the dronedarone and amiodarone initiators. After matching, the differences between the dronedarone and amiodarone initiatorss in the predefined covariates was no longer significant. This was especially seen for the history of CHF. Prior to PSM, dronedarone and amiodarone initiators had CHF rates of 18.8% and 42.0%, respectively, compared with 21.4% and 21.3% after PSM. Likewise, the distribution of the predefined covariates was well balanced in the PSM cohort for the other outcomes of interest after matching (data not shown).

Table 11 displays the hazard ratios of CV events, stroke, ILD, and ALI by drug exposure group in the PSM cohort. Among patients without a history of CHF, the PSM models showed a significantly higher risk of CV events (adjusted HR= 2.1, 95%CI: 1.2-3.7), stroke (adjusted HR= 1.8, 95%CI: 1.0-3.5), and CHF (adjusted HR=2.8, 95%CI: 2.0-3.9) in the amiodarone than in the dronedarone initiators, but not in the other antiarrhythmic groups which was in agreement with results of the traditional covariate adjustment. Among patients with a history of CHF, no statistically significant differences in HRs of the outcome events were found between dronedarone initiators and other antiarrhythmic drug initiators in the PSM cohort, which was also consistent with the findings in the traditional cohort.patients with former use of antiarrhythmics at baseline

Table 12 shows adjusted HRs of outcomes of interest in the patients with former use of antiarrhythmics. After adjustment for former use of antiarrhythmics and other covariates, a higher risk of CV events (adjusted HR= 1.8, 95%CI: 1.1-3.1) was found in the amiodarone than in the dronedarone intiatiors. The trends remained after stratification by CHF history (adjusted HR=2.1, 95%CI: 0.7-6.1 in patients with CHF history and 1.8, 95%CI: 1.0-3.3 in those without). No statistically different risk of stroke was observed across the exposure groups. The findings of the other outcomes were consistent with the results of primary analyses in general, although in the patients with former use of antiarrythmics, the risk of ILD in amiodarone users was more than 10 times higher (adjusted HR=10.9 (95%CI: 1.4-82.7) than in dronedarone users.

Discussion

The present observational study used data in real clinical practice setting to compare dronedarone with amiodarone, and other antiarrthythmic drugs in AF/AFL patients. In the absence of a history of heart failure, dronedarone was associated with a lower risk of CV events, including stroke, compared to amiodarone, and was similar to other antiarrhythmics. These results are consistent with another real-life study based on data obtained from federal health care databases including Medicare & Medicaid Services (CMS), Department of Defense (DoD), and Department of Veterans Affairs (VA), showing that heart failure risk did not increase within 30 days

Table 8: Adjusted hazard ratios of CV events, stroke, ILD and ALI by history of ventricular arrhythmia status (reference group: dronedarone)

	Amiodarone	Sotalol	Flecainide	Propafenone
Patients with ventricular arrhythmia at baseline				
CV events	1.1 (0.6-2.2)	0.5 (0.2-1.3)	0.3 (0.1-1.2)	0.3 (0.1-1.3)
Stroke	1.1 (0.5-2.5)	0.8 (0.3-2.1)	0.4 (0.1-1.7)	0.5 (0.1-2.1)
ILD	1.3 (0.3-5.0)	0.7 (0.1-4.0)	No cases	1.5 (0.2-9)
ALI	No cases	No cases	No cases	No cases
CHF	6.6 (2.5-17.3)	2.2 (0.8-6.2)	1.6 (0.5-5)	1.1 (0.3-4.3)
Patients without ventricular arrhythmia at baseline				
CV events	1.9 (1.2-3.0)	1.3 (0.8-2.2)	1.1 (0.6-2.1)	1.3 (0.7-2.3)
Stroke	2.5 (1.4-4.4)	1.6 (0.8-3.1)	1.7 (0.8-3.4)	1.9 (0.9-3.9)
ILD	1.0 (0.5-2.0)	1.2 (0.5-2.7)	0.6 (0.2-1.8)	0.5 (0.1-1.7)
ALI	1.7 (0.6-4.9)	0.2 (0.0-2.1)	0.5 (0.1-2.8)	1.8 (0.5-6.5)
CHF	2.3 (1.7-3.2)	1.0 (0.7-1.5)	0.7 (0.4-1.0)	0.8 (0.5-1.2)

Proportional hazard model, adjusted for age, gender, cohort entry year, number of AF/AFL diagnosis, congestive heart failure, MI, stroke, diabetes, hypertension, and dyslipidemia during baseline period

Table 9: Adjusted hazard ratios of CV events, stroke, ILD and ALI by history of left ventricular dysfunction status (reference group: dronedarone)

		Amiodarone	Sotalol	Flecainide	Propafenone
Patients with left ventricular dysfunction at baseline	CV events	2.8 (0.3-23.9)	N/A	N/A	N/A
	Stroke	N/A	N/A	N/A	N/A
	ILD	N/A	N/A	N/A	N/A
	ALI	N/A	N/A	N/A	N/A
	CHF	1.0 (0.2-5.6)	0.5 (0.1-3.6)	N/A	1.1 (0.1-14.9)
Patients without left ventricular dysfunction at baseline	CV events	1.6 (1.1-2.3)	1.0 (0.7-1.6)	0.9 (0.5-1.5)	1.0 (0.6-1.6)
	Stroke	1.9 (1.2-3.0)	1.3 (0.7-2.2)	1.2 (0.6-2.1)	1.4 (0.7-2.5)
	ILD	0.9 (0.5-1.8)	1.0 (0.5-2.1)	0.6 (0.2-1.6)	0.7 (0.2-1.9)
	ALI	1.8 (0.6-5.2)	0.2 (0.0-2.0)	0.9 (0.2-3.7)	2.3 (0.7-7.6)
	CHF	2.7 (2.0-3.7)	1.1 (0.8-1.6)	0.8 (0.5-1.2)	0.8 (0.5-1.3)

Proportional hazard model, adjusted for age, gender, cohort entry year, number of AF/AFL diagnosis, congestive heart failure, MI, stroke, diabetes, hypertension, and dyslipidemia during baseline period

Table 10: Characteristics of the study cohort during baseline period for the cardiovascular events after propensity score matching

	Before matching			After matching at 0.01 propensity score		
Pre-defined covariate	Dronedarone	Amiodarone	P value	Dronedarone	Amiodarone	P value
	(N=1,727)	(N=2,782)		(N=1,511)	(N=1,511)	
Age years mean (SD)	61 (10.7)	64 (11.8)	<.0001	62 (10.9)	61 (11.7)	0.49
Male (%)	1,206 (69.8)	2,013 (72.4)	0.07	1,072 (71.0)	1,055 (70.0)	0.5
Cohort entry yr 2009 (%)	396 (22.9)	1,044 (37.5)	<.0001	387 (25.6)	394 (26.1)	0.77
# of AF/AFL Dx mean (SD)	6 (5.5)	7 (5.7)	0.005	7 (5.5)	7 (6.0)	0.24
Hypertension (%)	1,232 (71.3)	2,116 (76.1)	0.0004	1,104 (73.0)	1,109 (73.4)	0.84
CHF (%)	325 (18.8)	1,168 (42.0)	<.0001	325 (21.5)	316 (20.9)	0.67
Diabetes (%)	392 (22.7)	883 (31.7)	<.0001	375 (24.8)	367 (24.3)	0.74
Dyslipidemia (%)	490 (28.4)	837 (30.1)	0.22	440 (29.1)	449 (29.7)	0.72
Ventricular arrhythmia (%)	687 (24.7)	333 (19.3)	<0.0001	303 (20.1)	296 (20.0)	0.75

in new users of dronedarone compared to amiodarone in patients without a history of heart failure prior to first prescription, Instead, the study found that dronedarone was associated with about 30% lower risk of heart failure than amiodarone (9). In align with the above findings, another propensity-score matched observational cohort study using administrative claims data between 1/1/2007-9/30/2011 from the HealthCore also showed amiodarone use was associated with higher incidence rate of new onset heart failure, heart failure hospitalizations, and TIA compared to dronedarone (Incidence rate ratio = 1.61, 1.39, and 2.01 respectively, all p values <0.05) as identified from claims (10). To date, no other published epidemiological studies have investigated the risk of CV events, stroke, ILD, and severe ALI in dronedarone users in comparison with the use of other antiarrhythmic.

This study showed that risk of ILD was not statistically different between dronedarone and the other antiarrhythmic drug initiators. It is possible that, since the follow-up time of the study was short (less than 1.5 years), it might be too short to observe a difference in the ILD risk between dronedarone and amiodarone. Indeed, in the sensitivity analyses among patients with both former use of antiarrhythmics and CHF at baseline, amiodarone was associated with about 11 times higher risk of ILD than dronedarone. The higher risk of ILD in the amiodarone users may be explained by the possible long-term use of amiodarone as indicated by that 86% of amiodarone patients had previous use of amiodrone before cohort entry (see Table 1), while patients with CHF history are usually sicker and may have had arrhythmia with antiarrhythmic drug treatment (in this case, amiodarone) for a long time period. A number of studies have showed that amiodarone can induce pulmonary toxicity. Pulmonary toxicity induced by amiodarone includes acute airways and lung diseases, sub-acute lung disease and pleural disease.[16-21] In the ATHENA clinical trial, 5 cases of ILD were reported out of 2,291 patients in dronedarone arm, which was not different from the reports in placebo arm (5 out of 2,313 subjects).[2] In other clinical trials who received dronedarone in ANDROMEDA, ADONIS, and EURIDIS trials, no cases of ILD or pulmonary toxicity were identified .[22,23] Our data support the available evidence in the literature that dronedarone users do not have an increased risk of ILD, unlike those using amiodarone. Although dronedarone has a similar electrophysiological profile to amiodarone, it is believed to be less likely to cause ILD because it contains a methane-sulfonamyl group which makes it less lipophilic, a shorter half-life, and a lower degree of tissue accumulation than amiodarone.[24]

The present study showed no statistical difference between dronedarone and the other antiarrhythmic initiators regarding risk of ALI, even though the risk of ALI tended to be higher in the amiodarone initiators (adjusted HR= 2.2, 95%CI: 0.8-6.2). On one hand, dronedarone might be less lipophilic with a shorter half-life and a lower degree of tissue accumulation as aforementioned. On the other hand, in recognition of the post-marketing spontaneously reported events of ALI in association with the dronedarone use,[4] further safety monitoring of ALI amongst dronedarone users may be warranted.

Of note, the above results observed in a cohort with traditional covariate adjustment were consistent with the ones in the matched cohort analyses on propensity score. The PSM technique[12] has been frequently used to minimize the potential bias in observational studies given that traditional covariate adjustment is often criticized for residual confounding bias by indication. Indeed, distribution of the covariates in the PSM cohort was more balanced after matching

Table 11: Hazard ratios of CV events, stroke, ILD and ALI by history of CHF with propensity-score matched dronedarone cohort as the reference

	Amiodarone	Sotalol	Flecainide	Propafenone
All patients				
CV events	1.7 (1.1-2.6)	1.0 (0.6-1.6)	1.2 (0.6-2.3)	0.9 (0.5-1.8)
Stroke	2.2 (1.3-3.7)	1.3 (0.7-2.3)	1.2 (0.6-2.5)	1.1 (0.6-2.3)
ILD	0.7 (0.3-1.6)	0.9 (0.4-1.9)	0.5 (0.2-1.5)	1.0 (0.3-3.5)
ALI	2.0 (0.7-6.0)	0.2 (0.0-1.6)	2.7 (0.3-26.2)	2.4 (0.5-12.4)
Patients with history of CHF				
CV events	1.2 (0.6-2.4)	0.3 (0.1-0.8)	1.7 (0.1-31.4)	0.5 (0.1-2.1)
Stroke	1.6 (0.6-4.1)	0.7 (0.2-2.3)	No cases	2.6 (0.3-27.7)
ILD	1.2 (0.4-4.0)	0.6 (0.1-2.8)	2.5 (0.2-36.1)	No cases
ALI	5.4 (0.6-45.4)	No cases	No cases	No cases
Patients without history of CHF				
CV events	2.1 (1.2-3.7)	1.4 (0.8-2.6)	1.2 (0.6-2.4)	1.1 (0.5-2.2)
Stroke	1.8 (1.0-3.5)	1.2 (0.6-2.5)	1.3 (0.6-2.8)	1.1 (0.5-2.7)
ILD	0.7 (0.3-2.1)	1.2 (0.4-3.1)	0.5 (0.1-2.3)	1.1 (0.3-4.3)
ALI	1.5 (0.4-5.4)	0.2 (0.0-1.5)	1.4 (0.2-8.7)	1.6 (0.3-9.6)
CHF	2.8 (2.0-3.9)	1.2 (0.8-1.8)	0.8 (0.5-1.3)	0.9 (0.5-1.4)

Matched propensity score on age, gender, cohort entry year, number of AF/AFL diagnosis, congestive heart failure, MI, stroke, diabetes, hypertension, dyslipidemia, and ventricular arrhythmia during baseline period

which might indicate possible advantages to reduce over-adjustments and/or residual confounding than the traditional method of covariate adjustment. Since the consistent findings were also found in the other sensitivity analyses with adjustment for history of ventricular arrhythmia, the sensitivity analyses with adjustment for history of left ventricular dysfunction, the sensitivity analyses of Cox regression among patients with former use of antiarrhythmic drug, the traditional covariate adjustment in our study with the new user design appeared to have controlled for confounding related to the predefined covariates and reasonable construct validity.

One of the limitations in the present study is that the codes for cardiovascular and liver injury outcomes selected for this study had relatively low sensitivities even though they had been validated in other studies with good specificities and positive predictive values (PPVs) .[5-8] The tradeoff of the sensitivity for better specificity with these selected codes may potentially have resulted in underestimate of the true extent of the disease. For the ILD, despite the diagnosis codes in this study were used in previous studies,[9] the validation of the codes are yet to be determined to reduce possible misclassification of the outcome. Even with the validated codes, a potential bias related to misclassification of outcome events was possible due to low or lack of sensitivity for reporting of possible adverse events with ICD-9 or CPT codes in the real world clinical setting in the insurance claims database. Another limitation is the possible residual confounding effect due to underlying conditions associated with prescription preferences. Finally, the number of patients with CHF is relatively small in this study. Therefore, the caution should be given to the interpretation of the findings in these patients.

The strengths of the present study include that it was based on the prerecorded claims in a large scale dataset of real-world clinical practices which had minimal recall bias. Furthermore, the new-user design of this study has also eliminated the survival bias related to prevalent users who had "survived" from the early period of pharmacotherapy. Meanwhile, the new user design may have also reduced the channeling bias that could have occurred due to the historical experience with other antiarrhythmics use before cohort entry.[25]

Table 12 Adjusted hazard ratios of CV events, stroke, and ILD by history of CHF in patients with former use of antiarrhythmics (reference group: dronedarone)

	Amiodarone	Sotalol	Flecainide	Propafenone
All patients				
CV events	1.8 (1.1-3.1)	1.0 (0.6-1.8)	1.5 (0.8-3.0)	1.6 (0.8-3.3)
Stroke	1.5 (0.9-2.7)	1.1 (0.6-2.1)	1.7 (0.8-3.6)	1.7 (0.8-3.8)
ILD	1.5 (0.8-2.8)	0.4 (0.2-0.8)	0.4 (0.2-1.2)	0.5 (0.2-1.3)
Patients with CHF				
CV events	2.1 (0.7-6.1)	1.5 (0.4-5.3)	1.2 (0.2-6.8)	1.6 (0.2-10.3)
Stroke	1.3 (0.5-3.5)	0.8 (0.2-2.7)	0.7 (0.1-4.3)	1 (0.1-6.9)
ILD	10.8 (1.4-81.9)	No cases	0.5 (0.0-10.1)	7.2 (0.6-93.2)
Patients without CHF				
CV events	1.8 (1.0-3.3)	0.9 (0.5-1.8)	1.6 (0.7-3.2)	1.6 (0.7-3.3)
Stroke	1.7 (0.8-3.5)	1.3 (0.6-2.7)	2.0 (0.9-4.7)	2.0 (0.8-4.7)
ILD	0.7 (0.3-1.4)	0.4 (0.2-1.0)	0.6 (0.2-1.7)	0.3 (0.1-0.9)
CHF	1.7 (1.2-2.4)	0.7 (0.4-1.0)	0.4 (0.3-0.7)	0.4 (0.2-0.6)

Outcome ALI was not included in the table because no cases were found in dronedarone initiators
Proportional hazard model, adjusted for age, gender, cohort entry year, number of AF/AFL diagnosis, congestive heart failure, MI, stroke, diabetes, hypertension, dyslipidemia, and ventricular arrhythmia during baseline period

Conclusions:

Compared to dronedarone, amiodarone was associated with higher risks of CV events and stroke, which were evident in patients who did not have a history of CHF, but not in their counterpart, indicating dronedarone could be an alternative therapy option with lower CV risk than amiodarone for the patients without a history of CHF. The risks of CV events, stroke, CHF, ILD, and ALI were not statistically different between dronedarone and the other antiarrhythmic groups. Caution should be exercised when interpreting the results due to the limitations based on the claims data, especially in patients with CHF history due to relatively small sample size Further investigations may be needed to further evaluate the risk of the events in relation to dronedarone and other anti-arrhythmics in the AF/AFL population, especially in the patients with certain underlying conditions such as left ventricular dysfunction, as well as their relative effectiveness.

References:

1. Clinformatics™ Data Mart. Eden Prairie: Optum. (http://www.optuminsight.com/life-sciences/solutions/value-strategy/marketing-analytics/clinformatics-data-mart/~/media/Ingenix/Life_Sciences/Documents/OptumInsightLifeSciencesClinformaticsDataMart.pdf). (Accessed March 1 2013).
2. Hohnloser SH, Crijns HJ, van Eickels M, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. N Engl J Med 2009;360(7):668-678.
3. Connolly SJ, Camm AJ, Halperin JL, et al. Dronedarone in high-risk permanent atrial fibrillation. N Engl J Med 2011;365(24):2268-2276.
4. Multaq prescribing information. (http://products.sanofi.us/multaq/multaq.html). (Accessed March 1 2013).
5. Myers RP, Leung Y, Shaheen AA, et al. Validation of ICD-9-CM/ICD-10 coding algorithms for the identification of patients with acetaminophen overdose and hepatotoxicity using administrative data. BMC Health Serv Res 2007;7:159.
6. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005;43(11):1130-1139.
7. Carson JL, Dufi A, Strom BL. Drug-Induced Acute Liver Disease. Pharmacoepidemiology and Drug Safety 1993;2:s19-s23.
8. Birman-Deych E, Waterman AD, Yan Y, et al. Accuracy of ICD-9-CM codes for identifying cardiovascular and stroke risk factors. Med Care 2005;43(5):480-485.
9. Zornberg GL, Hsu L, Dong D, et al. Dronedarone or Amiodarone and Risk of Heart Failure (HF): A Federal Partners Collaboration (FPC). Pharmacoepidemiology and Drug Safety, 2011; 20: S1–S364
10. Gosia Sylwestrzak G, Liu J, Rosenberg A et al. New Onset Heart Failure and Adverse Ischemic Events Associated with Amiodarone and Dronedarone Use among Atrial Fibrillation Patients Circ Cardiovasc Qual Outcomes. 2013; 6: A205
11. Jones N, Schneider G, Kachroo S, et al. A systematic review of validated methods for identifying pulmonary fibrosis and interstitial lung disease using administrative and claims data. Pharmacoepidemiol Drug Saf 2012;21 Suppl 1:256-260.
12. Seeger JD, Williams PL, Walker AM. An application of propensity score matching using claims data. Pharmacoepidemiol Drug Saf 2005;14(7):465-476.
13. Parsons LS, Group OR. Reducing bias in a propensity score matched-pair sample Using Greedy matching techniques. SUGI 2001;26:214-216.
14. Li Q, Glynn R, Dreyer N, et al. Validity of claims-based definitions of left ventricular systolic dysfunction in Medicare patients. Pharmacoepidemiology and Drug Safety 2011; 20: 700–708.
15. The Health Insurance Portability and Accountability Act of 1996 (HIPAA)

Privacy and Security Rules. (http://www.hhs.gov/ocr/privacy/). (Accessed March 1 2013).
16. Papiris SA, Triantafillidou C, Kolilekas L, et al. Amiodarone: review of pulmonary effects and toxicity. Drug Saf 2010;33(7):539-558.
17. Magro SA, Lawrence EC, Wheeler SH, et al. Amiodarone pulmonary toxicity: prospective evaluation of serial pulmonary function tests. J Am Coll Cardiol 1988;12(3):781-788.
18. Dusman RE, Stanton MS, Miles WM, et al. Clinical features of amiodarone-induced pulmonary toxicity. Circulation 1990;82(1):51-59.
19. Yamada Y, Shiga T, Matsuda N, et al. Incidence and predictors of pulmonary toxicity in Japanese patients receiving low-dose amiodarone. Circ J 2007;71(10):1610-1616.
20. Ernawati DK, Stafford L, Hughes JD. Amiodarone-induced pulmonary toxicity. Br J Clin Pharmacol 2008;66(1):82-87.
21. Singh SN, Fletcher RD, Fisher SG, et al. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. N Engl J Med 1995;333(2):77-82.
22. Singh BN, Connolly SJ, Crijns HJ, et al. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. N Engl J Med 2007;357(10):987-999.
23. Kober L, Torp-Pedersen C, McMurray JJ, et al. Increased mortality after dronedarone therapy for severe heart failure. N Engl J Med 2008;358(25):2678-2687.
24. Hughes PJ, Freeman MK, Cohenour FV, et al. Dronedarone: an alternative to amiodarone? Consult Pharm 2010;25(9):555-569.
25. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol 2003;158(9):915-920.