EPIDEMIOLOGY STUDY REPORT

Concomitant Use of Dronedarone and Digoxin (or Statins) and the Risk of Digitalis Intoxication (or Rhabdomyolysis and Myopathy)

- A Post-marketing Cohort Study Using the US Clinformatics DataMart® (formerly LabRx®) Database

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STUDY SYNOPSIS

Drug name:	Dronedarone (MULTAQ®)
Title:	Concomitant use of dronedarone and digoxin (or statins) and the risk of digitalis intoxication (or rhabdomyolysis and myopathy)-- a post-marketing cohort study using the US Clinformatics DataMart® (formerly LabRx®) database
Background:	The pharmacokinetic and possible pharmacodynamic drug-drug interactions with digoxin and statins have been identified to require precautionary statements included in the labeling. This study is part of the pharmacovigilance activity to further evaluate the potential interactions between dronedarone and digoxin or statins.
Objective(s):	To evaluate if the concomitant use of dronedarone increases the risk of dose-related digitalis intoxication in digoxin users and the risk of rhabdomyolysis and myopathy in statin users.
Study Design:	Retrospective cohort study
Study Population:	The study population consisted of 2 cohorts of patients identified from the Clinformatics DataMart® (formerly LabRx®) database who were at least 18 years old, had a diagnosis of atrial fibrillation (AF) or flutter (AFL), and filled a prescription of digoxin or statins between July 20, 2009 and March 31, 2016 (the date of the latest data available for this study). The cohort entry date was the date on which the first prescription of digoxin or statins was dispensed in the study period. Excluded from the cohort were the patients with the following conditions on the cohort entry date: 1) less than six months of enrollment period in the managed care organization (United Healthcare), and 2) a diagnosis of the outcome of interest within six months prior to the cohort entry date.

Exposure measurement:	Exposure of interest was concurrent use of dronedarone in digoxin or statins users. The concomitant use of dronedarone and digoxin (or statins) was defined as the treatment period during which a patient was on both drugs. Digoxin (or statins) alone was defined as the treatment period during which a patient was on digoxin (or statins), but not on dronedarone. The treatment duration on digoxin (or statins) alone began accumulating on the first day of digoxin (or statins) prescription and continued with the subsequent continuous digoxin (or statins) prescriptions until: 1) a prescription of dronedarone overlapping the digoxin (or statins) days supplied, or 2) the end of the digoxin (or statins) days supplied, 3) the occurrence of the outcome, 4) the enrollment end of membership, or 5) the end of the observation period (June 30, 2015), whichever came first. Likewise, the treatment duration of the concomitant use of dronedarone and digoxin (or statins) began on the first day of overlapping days supplied for dronedarone and digoxin (or statins) and finished at the end of overlapping treatment or the time of any other endpoints, whichever comes first. To account for potential non-adherence to medication, a grace period of up to 30 days was added to the days supplied for a drug when there were gaps between prescriptions.
Outcomes(s) of interest:	The respective outcomes of interest were digitalis intoxication in digoxin users and rhabdomyolysis/ myopathy in statin users. Digitalis intoxication was defined by the presence of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) codes 972.1 or E942.1 or tenth Revision, Clinical Modification (ICD-10) codes T46,xxxA or T46.0X5x. In a secondary analysis, the diagnosis of digitalis intoxication was defined as the presence of the above ICD-9 codes or ICD-10 codes plus a claim for laboratory testing for digoxin or hospitalization within 30 days of the diagnosis of digitalis intoxication. Rhabdomyolysis and myopathy were defined using a validated algorithm based on ICD-9 codes and corresponding ICD-10 codes, lab testing, and hospitalization.

Covariate(s):	The covariates in the multivariate analyses included age at baseline, gender, the number of diagnoses of AF/AFL and history of comorbidities including congestive heart failure (CHF), diabetes, hypertension, stroke, myocardial infarction, and renal failure within 180 days prior to a patient's cohort entry date, average dose of digoxin (or statins), the use of major medications with potent interactions with digoxin (or statins), and the calendar year of cohort entry date.
Statistical analysis:	The distributions of baseline risk factors in the concomitant dronedarone users and digoxin (or statins) alone users were summarized as percentages for categorical variables and as means or medians for continuous variables. The differences in the distributions of risk factors between the 2 comparison groups were tested using Pearson's chi-square test for categorical variables and Student's t-test or Wilcoxon rank-sum test for continuous variables. The crude incidence rate of the outcome of interest was calculated for each patient group. Cox proportional hazards regression models were fit to obtain hazard ratios for the outcome of interest for concomitant dronedarone use in comparison to the use of digoxin (or statins) alone adjusting for baseline risk factors.
Results:	The incidence rates of digitalis intoxication were 17.25 and 9.17 cases per 1,000 person-years (PY) in the concomitant dronedarone users (n=524) and the digoxin only users (n=32,459), respectively. The crude hazard ratio (HR) for digitalis intoxication for concomitant users compared to digoxin only users was 1.29 (95% CI: 0.41 – 4.05; p=0.66), and the adjusted HR was 1.56 (95% CI: 0.50 – 4.88; p=0.45). The association was weaker when a 7-day or no grace period was applied in sensitivity analyses. Furthermore, there were no cases of digitalis intoxication in the concomitant users when its definition required the presence of the ICD-9 codes or ICD-10 codes for digitalis intoxication and a claim for laboratory testing for digoxin or hospitalization within 30 days of the diagnosis. There were no cases of rhabdomyolysis/myopathy in the concomitant dronedadrone users (n=1,443), and the incidence rate of rhabdomyolysis/myopathy was 2.83 cases per 1,000 PY in the statin only users (n=103,020).

Conclusions:	There was a potential trend that the concomitant use of dronedarone among digoxin users was associated with an increased risk of digitalis intoxication. However, the association was not statistically significant. There was no evidence in this study to support that the concomitant use of dronedarone is associated with an increased risk of rhabdomyolysis or myopathy in statin users.

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ABBREVIATIONS

AF:	Atrial Fibrillation
AFL:	Atrial Flutter
CHF:	Congestive Heart Failure
CI:	Confidence Interval
HR:	Hazard Ratio
ICD-9:	International Classification of Diseases, Ninth revision
PY:	Person-Years

1 INTRODUCTION

Dronedarone (MULTAQ®), like amiodarone, is a multi-channel blocker displaying antiarrhythmic properties of all four Vaughan-William's classes. Although structurally related to amiodarone, dronedarone shows different relative effects on individual ion channels, and its structure was modified with the intent to eliminate the non-cardiovascular effects of amiodarone. Dronedarone has been shown to be effective for reduction of the risk of cardiovascular hospitalization or death in patients with AF/AFL at the dose of 400 mg BID. The efficacy and safety of dronedarone have been evaluated in a comprehensive non-clinical testing program and extensive comprehensive clinical program in compliance with the International Conference on Harmonization Good Clinical practice guidelines.

The continuous assessment of all potential risks of dronedarone during its development has identified that the drug may have potential interactions with digoxin and statins. The possible mechanism for the effect of dronedarone on digoxin is that dronedarone inhibits P-glycoprotein (P-gP) transport and results in increased digoxin plasma levels. The possible mechanisms for the effect of dronedarone on statins include: (1) dronedarone inhibits Cytochrome P450 3A4 (CYP3A4), thus the metabolism of substrates of this cytochrome (such as simvastatin, lovastatin and atorvastatin); (2) dronedarone inhibits the P-gP, which transport the same statins; and (3) dronedarone and/or its metabolites inhibit organic anion-transporting polypeptide (OATP) leading to increased exposure of statins transported by OATP such as rosuvastatin. Although managed appropriately during clinical trials, the potential risks of these interactions need to be monitored in dronedarone users in the real life setting. Such pharmacokinetic and possible pharmacodynamic drug-drug interactions with digoxin and statins have been identified to require adequate communication to the prescribing physicians through precautionary statements included in the labeling.

2 STUDY OBJECTIVES

To evaluate if the concomitant use of dronedarone increases the risk of dose-related digitalis intoxication in digoxin users and the risk of rhabdomyolysis and myopathy in statin users.

3 METHODS

3.1 STUDY DESIGN

This was a retrospective cohort study using existing data.

3.1.1 Source population/Database used

The data source was Clinformatics DataMart® (formerly LabRx®), an integrated medical and prescription claims database augmented with partial laboratory data for a segment of the population. As of March 2016 (the date of the latest data available for

this study), Clinformatics DataMart® consisted of about 15 year of data (since May 2000) and over 57 million unique members from 50 US states. On average, 15 million lives (active patients) are covered per year, comprising approximately 3 to 4% of the US population. In general, Clinformatics DataMart database is representative of the US general population in terms of age, gender and geographic region distributions. Since Clinformatics DataMart is an employment-based private insurance claims database, it has a lower proportion of patients aged 65+ years (9% in the Clinformatics DataMart vs. 12% in the US population).

3.1.2 Study population

The study population consisted of 2 cohorts (digoxin and statin cohorts) of patients identified from the Clinformatics DataMart® database who were at least 18 years old, had a diagnosis of atrial fibrillation (AF) or flutter (AFL), and filled a prescription of digoxin or statins between July 20, 2009 (the launch date of dronedarone in the US) and March 31, 2016. Statins of interest included atorvastatin, simvastatin, lovastatin, and pravastatin. Fluvastatin and rosuvastatin were not considered for potential interactions with dronedarone because they are not metabolized or only weakly metabolized by CYP3A4 and are not P-gP substrates. The cohort entry date was the date on which the first prescription of digoxin or statins was dispensed.

Excluded from the cohort were the patients with the following conditions on the cohort entry date: (1) less than 6 months of enrolment period in the managed care organization (United Healthcare), and (2) a diagnosis of the outcome of interest within six months prior to the cohort entry date.

3.2 EXPOSURE MEASUREMENT

The exposure of interest was concomitant use of dronedarone in digoxin or statins users. The concomitant use of dronedarone and digoxin (or statins) was defined as the treatment period during which a patient was on both drugs. Digoxin (or statins) alone was defined as the treatment period during which a patient was on digoxin (or statins), but not on dronedarone.

The treatment duration on digoxin (or statins) alone began accumulating on the first day of digoxin (or statins) prescription and continued with the subsequent continuous digoxin (or statins) prescriptions until: (1) a prescription of dronedarone overlapping the digoxin (or statins) days supplied, (2) the end of the digoxin (or statins) prescription, (3) the occurrence of the outcome, (4) the enrollment end of membership, or (5) the end of the observation period (March 31, 2016), whichever came first. Likewise, the treatment duration of the concomitant use of dronedarone and digoxin (or statins) began on the first day of overlapping days supplied for dronedarone and digoxin (or statins) and finished at the end of overlapping treatment or the time of any other endpoints, whichever comes first. To account for potential non-adherence to medication, a grace period of up to 30 days was added to the days supplied for a drug.

3.3 OUTCOMES OF INTEREST

The outcome of interest for the digoxin cohort was digitalis intoxication. The diagnosis of digitalis intoxication was defined by the presence of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) codes 972.1 or E942.1 (Appendix 1)[1-3], or ICD-10 codes T46.xxxA or T46.0X5x (Appendix 1). In a secondary analysis, the diagnosis of digitalis intoxication was defined by the presence of ICD-9 codes 972.1 or E942, or ICD-10 codes T46.xxxA or T46.0X5x plus at least one laboratory testing claim for digoxin (Appendix 2) or hospitalization within 30 days of the diagnosis of digitalis intoxication.

The outcomes of interest for the statin cohort were rhabdomyolysis and myopathy. Rhabdomyolysis and myopathy were defined by an algorithm based on ICD-9 codes, lab testing, and/or hospitalization that have been validated in a published study (Appendix 3).[4] In addition, the ICD-10 codes (Appendix 4) were also used based on the mapping of the ICD-9 codes predefined.

3.4 COVARIATES

A number of potential confounders were considered in the multivariate analyses. These covariates included age at baseline, gender, cohort entry date, the number of diagnoses of AF/AFL within 180 days prior to a patient's cohort entry date, and the presence of comorbidities including congestive heart failure (CHF), diabetes, hypertension, stroke, myocardial infarction and renal failure within 180 days prior to a patient's cohort entry date (Appendix 5).

The use of major medications that have potent interactions with digoxin or statins was also adjusted for as a potential confounder. For digoxin, such medications included arbutamine, atazanavir, calcium chloride, calcium gluceptate, calcium gluconate and saquinavir.[5] For statins, such medications included erythromycin, clarithromycin, azithromycin, fusidic acid, warfarin, dicoumarol, nefazodone, ketoconazole, itraconazole, cholestyramine, mibefradil, digoxin, gemfibrozil, cyclosporine, chlorzoxazone and niacin.[6]

The average daily doses of digoxin and statins were calculated and treated as potential confounders in the analyses. A dose of each type of statin was calculated as the effective dose of pravastatin based on the findings that atorvastatin at the dose of 10 mg, simvastatin at 20 mg, lovastatin at 40 mg, and pravastatin at 40 mg are equally effective in lowering cholesterols. [7, 8]

4 STATISTICAL ANALYSIS

Univariate analyses were performed to describe the distributions of baseline risk factors in the concomitant dronedarone users and digoxin (or statins) alone users separately. Percentages for categorical variables and means or medians for continuous variables were calculated. The differences in the distributions of risk factors between the 2 comparison groups were then tested using Pearson's chi-square test for percentages, Student's t-test for means, and Wilcoxon rank-sum test for medians.

The crude incidence rate and its 95% confidence interval (CI) of the outcome of interest were calculated for each patient group. Cox proportional hazards regression models were fit to obtain crude hazard ratios and their 95% CIs for the outcome of interest for concomitant dronedarone use in comparison to the use of digoxin (or statins) alone. In multivariate analyses, adjusted hazard ratios and their 95% CIs were obtained by fitting Cox proportional hazards models adjusting for baseline risk factors.

To examine the impact of the use of grace period to account for gaps between prescriptions on the results, sensitivity analyses were also conducted by using a 7-day grace period and without using any grace period.

All statistical analyses were conducted in SAS version 9.3 (SAS Institute, Cary, NC). All tests for statistical significance were two-sided at α=0.05 level.

5 RESULTS

5.1 Concomitant use of dronedarone in digoxin users

In the digoxin cohort, 32,459 patients had used digoxin alone, and 524 patients had concomitantly used dronedarone between July 20, 2009 and March 31, 2016. In comparison, the 6th interim report using the data as of June 30, 2015 included 30,679 patients who had used digoxin alone and 510 patients who had concomitantly used dronedarone.

Table 1 shows that the concomitant users were younger, had more medical encounters listing AF/AFL as a diagnosis in the 180 days prior to cohort entry, were less likely to have diabetes, but were more likely to have hypertension.

Table 2 shows that the incidence rates of digitalis intoxication were 17.25 and 9.17 cases per 1,000 person-years (PYs) in the concomitant dronedarone users and the digoxin only users, respectively. The crude hazard ratio (HR) for digitalis intoxication for concomitant users compared to digoxin only users was 1.29 (95% CI: 0.41 – 4.05; p=0.66), and the adjusted HR was 1.56 (95% CI: 0.50 – 4.88; p=0.45). When digitalis intoxication was defined by ICD-9 diagnosis codes plus claims for lab tests for digoxin or hospitalization within 30 days of diagnosis, there were no cases of digitalis intoxication in the concomitant users, and the incidence rate was 1.22 cases per 1,000 PY in the digoxin only users.

Table 3 presents the results of the sensitivity analyses using a 7-day grace period for gaps between prescriptions. The incidence rates of digitalis intoxication were 10.45 and 9.96 cases per 1,000 PY in the concomitant users and the digoxin only users, respectively. The crude HR for digitalis intoxication was 0.70 (95% CI: 0.10 – 4.97; p=0.72), and the adjusted HR was 0.81 (95% CI: 0.11 – 5.83; p=0.84). When digitalis intoxication was defined by ICD-9 diagnosis codes plus claims for lab tests for digoxin or hospitalization within 30 days of diagnosis, there were no cases of digitalis intoxication in the concomitant users, and the incidence rate was 1.51 cases per 1,000 PY in the digoxin only group.

Table 4 presents the results of the sensitivity analyses when no grace period was used for gaps between prescriptions. The incidence rates of digitalis intoxication

were 16.86 and 13.67 cases per 1,000 PY in the concomitant users and the digoxin only users, respectively. The crude HR for digitalis intoxication was 0.96 (95% CI: 0.13 – 6.83; p=0.96), and the adjusted HR was 1.14 (95% CI: 0.16 – 8.16; p=0.89). When digitalis intoxication was defined by ICD-9 diagnosis codes and/or ICD-10 codes plus claims for lab tests for digoxin or hospitalization within 30 days of diagnosis, there were no cases of digitalis intoxication in the concomitant users and the incidence rate was 1.77 cases per 1,000 PY in the digoxin only users.

5.2 Concomitant use of dronedarone in statin users

In the statin cohort, 103,020 patients had used statins alone, and 1,443 patients had concomitantly used dronedarone between July 20, 2009 and March 31, 2016. In comparison, the 6th interim report using the data as of June 30, 2015 included 94,371 patients had used statins alone, and 1,349 patients had concomitantly used dronedarone.

Table 5 shows that the concomitant users were younger, had more medical encounters listing AF/AFL as a diagnosis in the 180 days prior to cohort entry, were more likely to have hypertension, but were less likely to have diabetes, stroke, congestive heart failure, and myocardial infarction.

Table 6 shows that there were no cases of rhabdomyolysis/ myopathy in the concomitant users regardless of the grace period used, and the incidence rate of rhabdomyolysis/ myopathy was 2.83 cases per 1,000 PY in the statin only users. When a 7-day grace period was used for gaps between prescriptions, the incidence rate of rhabdomyolysis/ myopathy was 2.62 cases per 1,000 PY in the statin only users (Table 7). When no grace period was added for gaps between prescriptions, the incidence rate of rhabdomyolysis/myopathy was 2.68 cases per 1,000 PY (Table 8).

6 DISCUSSION

This study found that compared to digoxin use alone, there was a trend that the concomitant use of dronedarone was associated with an increased risk of digitalis intoxication (adjusted HR = 1.56, 95% CI, 0.50 – 4.88; P=0.45), when a grace period up to 30 days was added to account for gaps between prescriptions. However, this association was not statistically significant. The association was weaker when a 7-day grace period or no grace period was applied. As for the concomitant use of dronedarone and statins, there were no cases of rhabdomyolysis and myopathy among the concomitant users.

Understanding the strengths and limitations of this study is helpful when interpreting its results. As for strengths, first, this study was able to examine the interactions between dronedarone and digoxin or statin using data collected from real-world practice. Second, the database included a large number of patients. Meanwhile, this study has a few limitations. First, the data were limited to patients enrolled in employment-based health plans, thus the patients were likely to be slightly younger than the general patient population. Second, the database consisted of medical and prescription claims, therefore there was a lack of data on indications for prescription, compliance, and in-hospital prescription data. Furthermore, the label of dronedarone

recommends adjusting doses of digoxin and statins in case of co-administration. But such adjustments, which may reduce the risk of digitalis intoxication or rhabdomyolysis/ myopathy, were not captured in the database. Third, there were no detailed clinical data, e.g., type of AF/AFL and severity of disease available in the database used in this study. Fourth, there could be residual confounding because of unmeasured and unavailable confounders, e.g., severity of congestive heart failure and obesity. Last, although this study used the data of a large number of patients, the numbers of outcomes in the concomitant dronedarone users were small. Therefore, the confidence intervals of the adjusted HRs were wide, indicating a lack of precision in estimating the HRs. Thus, it is important to note that with a limited number of users included in the final study report, the study results must be interpreted with caution.

7 CONCLUSIONS

This study found a trend that the concomitant use of dronedarone among digoxin users was associated with an increased risk of digitalis intoxication. However, the association was not statistically significant.

In addition, there was no evidence in this study to support that the concomitant use of dronedarone is associated with an increased risk of rhabdomyolysis or myopathy in statin users.

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9 TABLES AND FIGURES

Table 1 - Characteristics of patients treated by digoxin alone or in combination with dronedarone at baseline (N=32,983).*

Risk Factor	Digoxin Alone (N=32,459)	Digoxin and dronedarone (N=524)	p Value
Age (y), Mean±SD	65.1±12.2	62.7±11.1	<0.0001
Age group (y), n (%)			<0.0001
18-29	173(0.5)	2(0.4)	
30-39	547(1.7)	12(2.3)	
40-49	2100(6.5)	33(6.3)	
50-59	7510(23.1)	150(28.6)	
60-69	11064(34.1)	199(38.0)	
70-79	5284(16.3)	81(15.5)	
>=80	5781(17.8)	47(9.0)	
Female, n (%)	11561(35.6)	196(37.4)	0.40
No. of diagnoses of atrial fibrillation or atrial flutter, median (lower, upper quartiles) †	4 (1, 7)	7 (4,12)	<0.0001
History of comorbidities†			
Congestive heart failure, n (%)	11388(35.1)	163(31.1)	0.06
Diabetes, n (%)	9625(29.7)	135(25.8)	0.05
Hypertension, n (%)	22125(68.2)	396(75.6)	0.0003
Stroke, n (%)	2290(7.1)	33(6.3)	0.50
Myocardial infarction, n (%)	1487(4.6)	22(4.2)	0.68
Renal failure, n (%)	1000(3.1)	11(2.1)	0.20
Average dose of digoxin (mg), mean±SD	189.7±76.3	186.0±68.8	0.27
Use of major medications with potent interactions with digoxin, n (%) ‡.	8(0)	0(0)	0.72
Cohort entry year, n (%)			<0.0001
7/20/2009 – 12/31/2009	10901(33.6)	42(8.0)	
1/1/2010 – 12/31/2010	5371(16.5)	148(28.2)	
1/1/2011 – 12/31/2011	4397(13.5)	133(25.4)	
1/1/2012 – 12/31/2012	3560(11.0)	79(15.1)	
1/1/2013 – 12/31/2013	2887(8.9)	55(10.5)	
1/1/2014 – 12/31/2014	2619(8.1)	43(8.2)	
1/1/2015 - 12/31/2015	2323(7.2)	20(3.8)	
1/1/2016 – 3/31/2016	401(1.2)	4(0.8)	

Risk Factor	Digoxin Alone (N=32,459)	Digoxin and dronedarone (N=524)	p Value

* Plus–minus values are means±SD. Because of rounding, percentages may not total 100.
† 180 days prior to cohort entry date.
‡ Major medications included arbutamine, atazanavir, calcium chloride, calcium gluceptate, calcium gluconate, and saquinavir.

Table **2 - Risk of digitalis intoxication (30-day grace period for gaps between prescriptions)**

Outcome	Drug	Number of Patients	Person-Years	Number of Events	Incidence Rate (per 1,000 Person-Years, 95% CI)	Unadjusted Hazard ratio (95% CI)*	P Value	Adjusted Hazard ratio† (95% CI)*	p Value
Digitalis intoxication, claim-based diagnosis	Digoxin Alone	32459	32827.56	301	9.17 (8.13,10.20)	Reference	-	Reference	-
	Digoxin with Dronedarone	524	173.91	3	17.25 (0,36.77)	1.29(0.41,4.05)	0.66	1.56(0.50,4.88)	0.45
Digitalis intoxication, claim-based diagnosis confirmed by lab testing for digoxin or hospitalization	Digoxin Alone	32459	32868.64	40	1.22 (0.84,1.59)	Reference	-	Reference	-
	Digoxin with Dronedarone	524	174.1547	0	0 (0,0)	Not calculated	-	Not calculated	-

* CI denotes confidence interval.

† Risk factors adjusted for included age, sex, cohort entry year, and history of co-morbidities such as congestive heart failure, diabetes, hypertension, stroke, myocardial infarction, renal failure, number of AFL diagnosis during baseline and potential interaction drug use within study period.

Table 3 - Risk of digitalis intoxication (7-day grace period for gaps between prescriptions)

Outcome	Drug	Number of Patients	Person-Years	Number of Events	Incidence Rate (per 1,000 Person-Years, 95% CI)	Unadjusted Hazard ratio (95% CI)*	P Value	Adjusted Hazard ratio† (95% CI)*	p Value
Digitalis intoxication, claim-based diagnosis	Digoxin Alone	32556	21833.43	217	9.94 (8.62,11.26)	Reference	-	Reference	-
	Digoxin with Dronedarone	427	95.72	1	10.45 (0,30.92)	0.7(0.10,4.97)	0.72	0.81(0.11,5.83)	0.84
Digitalis intoxication, claim-based diagnosis confirmed by lab testing for digoxin or hospitalization	Digoxin Alone	32556	21853.59	33	1.51 (0.99,2.03)	Reference	-	Reference	-
	Digoxin with Dronedarone	427	95.77	0	0 (0,0)	Not calculated	-	Not calculated	-

* CI denotes confidence interval.

† Risk factors adjusted for included age, sex, cohort entry year, and history of co-morbidities such as congestive heart failure, diabetes, hypertension, stroke, myocardial infarction, renal failure, number of AFL diagnosis during baseline and potential interaction drug use with study period.

Table 4 - Risk of digitalis intoxication (no grace period for gaps between prescriptions).

Outcome	Drug	Number of Patients	Person-Years	Number of Events	Incidence Rate (per 1,000 Person-Years, 95% CI)	Unadjusted Hazard ratio (95% CI)*	p Value	Adjusted Hazard ratio† (95% CI)*	p Value
Digitalis intoxication, claim-based diagnosis	Digoxin Alone	32621	11854.67	162	13.67 (11.56,15.77)	Reference	-	Reference	-
	Digoxin with Dronedarone	362	59.32	1	16.86 (0,49.90)	0.96(0.13,6.83)	0.96	1.14(0.16,8.16)	0.89
Digitalis intoxication, claim-based diagnosis confirmed by lab testing for digoxin or hospitalization	Digoxin Alone	32621	11869.02	21	1.77 (1.01,2.53)	Reference	-	Reference	-
	Digoxin with Dronedarone	362	59.35	0	0 (0,0)	Not calculated	-	Not calculated	-

* CI denotes confidence interval.
† Risk factors adjusted for included age, sex, cohort entry year, and history of co-morbidities such as congestive heart failure, diabetes, hypertension, stroke, myocardial infarction, renal failure, number of AFL diagnosis during baseline and potential interaction drug use with study period.

Table 5 - Characteristics of patients treated by statins alone or in combination with dronedarone at baseline (N=104,463).*

Risk Factor	Statins Alone (N=103,020)	Statins and Dronedarone (N=1,443)	p Value
Age (y), Mean±SD	64.0±11.0	63.1±9.5	<0.0001
Age group (y), n (%)			<0.0001
18-29	111(0.1)	0(0)	
30-39	1103(1.1)	11(0.8)	
40-49	6828(6.6)	74(5.1)	
50-59	27000(26.2)	398(27.6)	
60-69	39528(38.4)	649(45.0)	
70-79	15683(15.2)	208(14.4)	
>=80	12767(12.4)	103(7.1)	
Female, n (%)	30860(30.0)	401(27.8)	0.07
No. of diagnoses of atrial fibrillation or atrial flutter, median (lower, upper quartiles) †	4 (5.0)	5.9(5.5)	<0.0001
History of comorbidities†			
Congestive heart failure, n (%)	22558(21.9)	275(19.1)	0.01
Diabetes, n (%)	33979(33.0)	426(29.5)	0.0055
Hypertension, n (%)	22125(21.5)	1149(79.6)	0.0021
Stroke, n (%)	9535(9.3)	99(6.9)	0.0018
Myocardial infarction, n (%)	7959(7.7)	84(5.8)	0.0070
Renal failure, n (%)	3646(3.5)	43(3.0)	0.2531
Average dose of statins (equivalent to pravastatin, mg), mean±SD	88.7±75.0	86.2±73.2	0.65
Use of major medications with potent interactions with statins, n (%) ‡	56788(55.1)	731(50.7)	0.0007
Cohort entry year, n (%)			<.0001
7/20/2009 – 12/31/2009	26359(25.6)	106(7.3)	
1/1/2010 – 12/31/2010	15259(14.8)	333(23.1)	
1/1/2011 – 12/31/2011	14333(13.9)	342(23.7)	
1/1/2012 – 12/31/2012	12014(11.7)	200(13.9)	
1/1/2013 – 12/31/2013	11233(10.9)	173(12)	
1/1/2014 – 12/31/2014	10559(10.2)	153(10.6)	
1/1/2015 - 12/31/2015	11209(10.9)	118(8.2)	
1/1/2016 – 3/31/2016	2054(2.0)	18(1.2)	

* Plus–minus values are means±SD. Because of rounding, percentages may not total 100.
† 180 days prior to cohort entry date.
‡ Major medications included erythromycin, clarithromycin, azithromycin, fusidic acid, warfarin, dicoumarol, nefazodone, ketoconazole, itraconazole, cholestyramine, mibefradil, digoxin, gemfibrozil, cyclosporine, chlorzoxazone, and niacin.

Table 6 - Risk of rhabdomyolysis and myopathy (30-day grace period for gaps between prescriptions).

Drug	Number of Patients	Person-Years	Number of Events	Incidence Rate (per 1,000 Person-Years, 95% CI)
Statins Alone	103020	112278.54	318	2.83 (2.52,3.14)
Statins with Dronedarone	1443	848.2	0	0 (0,0)

* CI denotes confidence interval. Hazard ratios were not calculated.

Table 7 - Risk of rhabdomyolysis and myopathy (7-day grace period for gaps between prescriptions).

Drug	Number of Patients	Person-Years	Number of Events	Incidence Rate (per 1,000 Person-Years, 95% CI)
Statins Alone	103159	68242.51	179	2.62 (2.24,3.01)
Statins with Dronedarone	1304	454.86	0	0 (0,0)

* CI denotes confidence interval. Hazard ratios were not calculated.

Table 8 - Risk of rhabdomyolysis and myopathy (no grace period for gaps between prescriptions).

Drug	Number of Patients	Person-Years	Number of Events	Incidence Rate (per 1,000 Person-Years, 95% CI)
Statins Alone	103332	35474.20	95	2.68 (2.14,3.22)
Statins with Dronedarone	1130	216.51	0	0 (0,0)

* CI denotes confidence interval. Hazard ratios were not calculated.

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10 APPENDICES

Appendix 1. ICD-9 or ICD-10 codes for digitalis intoxication.

ICD-9 Code	ICD-10 Code	Description
972.1	T46.0X1A, T46.0X2A,T46.0X3A, T46.0X4A	Poisoning by cardiotonic glycosides and drugs of similar action
E942.1	T46.0X5, T46.0X5A, T46.0X5D, T46.0X5S	Cardiotonic glycosides and drugs of similar action causing adverse effects in therapeutic use

Appendix 2. LOINC codes for testing for digoxin.

Drug	LOINC code
Digoxin	10535-3, 14698-5, 29216-9, 32067-1, 35244-3, 3562-6, 3563-4
Digitoxin	15104-3, 29215-1, 3304-3, 3559-2, 3561-8, 4221-8

Appendix 3. Algorithm for defining rhabdomyolysis and myopathy cases

	Description
1	any code of myoglobinuria (ICD-9 code 791.3) or rhabdomyolysis (ICD-9 code 728.88)
2	a primary code of "other disorders of muscle" (ICD-9 code 728.89)
3	a secondary code of "other disorders of muscle (ICD-9 code 728.89) plus any serum creatine kinase (CK) test (CPT codes: 82550, 82552, 82553, 82554, 80012, 80016, 80018, 80019) within 7 days of hospitalization/admission for the ICD-9 code 728.89
4	a secondary code of "other disorders of muscle (ICD-9 code 728.89) plus hospital discharge code for acute renal failure (ICD-9 code 584.x)

Appendix 4. Algorithm for defining rhabdomyolysis and myopathy cases

	Description
1	any code of myoglobinuria (ICD-10 code R82.1) or rhabdomyolysis (ICD-10 code M62.82)
2	a primary code of "other disorders of muscle" (ICD-10 code M62.89)
3	a secondary code of "other disorders of muscle (ICD-10 code M62.89) plus any serum creatine kinase (CK) test (CPT codes: 82550, 82552, 82553, 82554, 80012, 80016, 80018, 80019) within 7 days of hospitalization/admission for the ICD-10 code M62.89
4	a secondary code of "other disorders of muscle (ICD-10 code M62.89) plus hospital discharge code for acute renal failure (ICD-10 code N17, N17.1, N17.2, N17.8, N17.9)

Appendix 5. ICD-9 or ICD-10 codes for comorbidities.

Comorbidity	ICD-9 Code	ICD-10 Code
Congestive heart failure	428.XX,398.91,402.01,402.11,402.91,404.01,404.11,404.91,404.03,404.13,404.93	I50.2, I50.3, I50.4, I50.9, I09.81, I11, I13, I13.2
Diabetes	250.XX	E08, E10, E11, E13
Hypertension	401.XX-405.XX	I10, I11, I12, I13, I15, G93.2, I27.0, I87.3
Stroke	435.XX,438.XX,437.1X,437.9X,433.X1,434.X1	G45, I69.91, I67.81, I67.82, I67.89, I67.9, I63.139. I63.239, I63.019, I63.119, I63.219, I63.22, I63.59, I63.20, I63.30, I63.40, I63.50
Myocardial infarction	410.XX	I21.0, I21.1, I21.2, I21.3, I21.4
Renal failure	403.00,403.01,403.11,403.91,404.00,404.01,404.02,404.03,404.12,404.13,404.92,404.93,585.X,X586.XX	I12, I12.9, I13, I13.10, I13.11, I13.2, N18.x, N19