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Antiarrhythmic Drug Use in Patients <65 Years of Age With Atrial Fibrillation and Without Structural Heart Disease

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Abstract

Little is known in clinical practice about antiarrhythmic drug (AAD) use in atrial fibrillation (AF) patients (particularly younger ones) that do not have structural heart disease. Using the MarketScan® database, we identified patients <65 years of age without known coronary artery disease or heart failure who had an AAD prescription claim (Class Ic drug, amiodarone, sotalol, or dronedarone) after their first AF encounter. A multinomial logistic regression model was created to assess factors associated with using each available AAD, compared with using Class Ic drugs before and after dronedarone was marketed in the United States. Additionally, we used the Kaplan Meier method to determine the rates of change in AAD use and discontinuation during the year post-AAD initiation. Of 8562 AF patients, 35% received Class Ic drugs, 34% amiodarone, 24% sotalol, and 7% dronedarone. The median patient age was 56 (IQR 49, 61) and 34% were female. Both before and after dronedarone was marketed, there was a statistically significant lower likelihood of Class Ic drug use versus other AAD use with increasing age, inpatient index AF encounter, and prior or concomitant anticoagulation therapy. During the 1 year post-AAD initiation, the AAD change rate was 14% for Class Ic drugs, 8% amiodarone, 17% sotalol, and 18% dronedarone ($p<0.001$); the AAD discontinuation rate was 40% for Class Ic drugs, 52% amiodarone, 40% sotalol, and 69% dronedarone ($p<0.001$). In conclusion, we found extensive use of amiodarone that may be inconsistent with guideline recommendations, and unexpectedly high rates of AAD discontinuation.

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Keywords

antiarrhythmic drug use; atrial fibrillation; younger patient population

The purpose of our study was to evaluate the use of Class Ic and Class III AAD in clinical practice among younger AF patients without concomitant CAD or heart failure. Factors associated with the selection of individual AADs were determined and longitudinal use of the initially selected AAD was explored during the 12 months following drug initiation.

Methods

The study cohort was obtained from the Thomas Reuters MarketScan® Commercial Claims and Encounters Database. This database consists of inpatient, outpatient, and prescription claims data from United States (U.S.) employers who provide health plans for their employees and employees' spouses and dependents. The MarketScan database has primarily been used for health care utilization and outcomes studies of a variety of diseases, including AF.¹⁻³ For purposes of this analysis, we obtained data on all patients with an inpatient or outpatient encounter that included a diagnosis of AF (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 427.31) between January 1, 2006 and December 31, 2010. The MarketScan database used for this study does not include claims data from patients <65 years of age. ICD-9-CM and current procedural terminology (CPT) codes for diagnosis and procedures of interest were obtained from previously published studies.⁴⁻⁶ This study was reviewed by the Duke University Health System Institutional Review Board (IRB) and determined to be exempt from IRB review.

We only included patients with available individual-level and pharmacy benefit data. We identified the first inpatient or outpatient encounter with a diagnosis of AF, and considered this the index AF encounter. We excluded patients without at least 6 months of continuous health plan enrollment prior to the "index AF encounter." Using National Drug Codes (NDCs), we selected patients who filled a prescription for a 30-day supply for oral formulations of Vaughan Williams Class Ic (propafenone, flecainide) and Class III (amiodarone, dofetilide, sotalol, and dronedarone) AAD within 14 days after the end of the index AF encounter; the date of this initial prescription claim was considered the "index AAD prescription date." Patients were then excluded from the final study cohort if they were <18 years of age, had a prescription claim for any AAD in the 6 months prior to the index AAD prescription, or had any of the following diagnoses in the 6 months prior to the index AAD prescription: CAD (ICD-9-CM codes 410 to 414, 429.2, V45.81); heart failure (ICD-9-CM codes 428.xx 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, and 398.91); cardiomyopathy (ICD-9-CM codes 425.0, 425.1, 425.2, 425.3, 425.5, 425.7, 425.8, 425.); ventricular arrhythmia (ICD-9-CM codes 427.1, 427.4x, 427.5); or heart transplant or left ventricular assist device (ICD-9-CM codes 37.5x, 33.6, 37.6x, V42.1).

The study cohort was divided into treatment groups based upon the index prescription: Class Ic drugs (propafenone or flecainide), amiodarone, dofetilide, sotalol, and dronedarone. Propafenone and flecainide were considered to be very similar in pharmacologic activity and indication; therefore, these two drugs were combined into one treatment group. The Class III

drugs were thought to be pharmacologically distinct; therefore, they were considered separate treatment groups. Since very few patients were prescribed dofetilide during the study period, the dofetilide treatment group was excluded from the study, leaving four main treatment groups: 1) Class Ic, 2) amiodarone, 3) sotalol, and 4) dronedarone.

Dronedarone was first marketed in the U.S. in July 2009. Being a new AAD, we recognized that the availability of dronedarone could differentially impact AAD drug selection before and after its marketing; consequently, the analyses of factors associated with Class Ic drugs versus each Class III drug were done in two distinct time periods: 1) before July 1, 2009; and 2) after June 30, 2009. Likewise, a separate multinomial logistic regression model was created for each time period. In the first model (index AAD prescriptions before July 1, 2009), we determined factors associated with amiodarone versus Class Ic drugs and sotalol versus Class Ic drugs. In the second model (index AAD prescriptions after June 30, 2009), we determined factors associated with amiodarone versus Class Ic, sotalol versus Class Ic, and dronedarone versus Class Ic. In each model, we used a backward selection process of variables.

Candidate variables for each model were the same and included: age; sex; inpatient versus outpatient index AF encounter; geographic region; AF as primary diagnosis versus secondary diagnosis; hospitalization in the 6 months prior to index prescription; year of index prescription; electrical cardioversion during index AF encounter; cardiac ablation during index AF encounter; number of days from index AF encounter to index prescription, rate-controlling drug use (beta-blocker, calcium channel blocker, or digoxin), QT-prolonging medication use,⁷ or anticoagulant use concomitant with or within 6 months prior to the index prescription; and, during the 6 month prior to the index prescription, a history of atrial flutter, bradyarrhythmias, other atrial arrhythmias, diabetes, hypertension, chronic or acute rheumatic heart disease, pacemaker, renal impairment, liver disease, thyroid disease, pulmonary disease, cancer, stroke, cerebral hemorrhage, depression, obesity, non-rheumatic valvular disease, bleeding, or cardiothoracic surgery. Continuous variables are presented as medians and 25th and 75th percentiles, and categorical variables are presented as percentages.

To evaluate longitudinal use following the index AAD prescription, we first assessed changes in AAD drug use in the 12 months following the index prescription in the overall study cohort. We determined initiation of another AAD treatment by the presence of a prescription claim for a 30-day supply of an AAD in a different group from the index AAD prescription (Class Ic, amiodarone, sotalol, dronedarone) during the 12 months after the index AAD prescription date. We used the Kaplan Meier method to determine rates and 95% confidence intervals (CIs) for rates of AAD change for each of the four treatment groups. Among patients without an AAD change, we explored discontinuation of the index AAD. Using the day's supply from each prescription claim of the index AAD, we identified gaps in prescription fills for the index AAD. A gap of 90 days during the 12 months following the index AAD prescription was considered a discontinuation of the index AAD. A prescription claim with a dispensed day supply of <0 days on any subsequent AAD prescription claim was considered a claim error, and the patient was excluded from our analysis.

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Results

After excluding a small number of patients who initially received dofetilide (n=46; Figure 1), a total of 8562 patients <65 years of age with AF, but without CAD or heart failure, were included in the final study cohort. In this final cohort, use of a Class Ic drugs was found in 35% of patients, followed by amiodarone (34%), sotalol (24%), and dronedarone (7%). Among those receiving a Class Ic drug, 51.5% received flecainide and 48.5% received propafenone. Of the 8562 patients in the overall study cohort, 5175 (60%) were prescribed their index AAD before July 1, 2009 and 3387 (40%) were prescribed their index AAD after June 30, 2009. Within each time period, the proportion of patients taking amiodarone and Class Ic drugs were nearly identical (Figure 1).

Patient characteristics of the overall study cohort and by time period (before July 1, 2009 and after June 30, 2009) are presented in Table 1. Overall, the median patient age was 56 (interquartile range [IQR] 49, 61) and 34% of patients were female. Approximately 69% of patients were hospitalized with their first identified AF encounter. Of those hospitalized for their index AF encounter, the median duration of hospitalization was 4 days (IQR 2, 7). Among those with a hospitalization for the index AF encounter, the length of stay was longer for those who received amiodarone than patients who received any of the other drugs (6 days for patients who received amiodarone versus 3 days for sotalol and dronedarone and 2 days for Class Ic drugs, $p<0.001$). The median time from index encounter (inpatient or outpatient) to the index prescription claim was 4 days (IQR 2, 7).

In the time period before dronedarone was marketed, Class Ic drugs were less likely to be used than amiodarone and sotalol as patient age increased, in patients with their index AF encounter as an inpatient versus outpatient visit, in patients with a history of diabetes, and in those with prior or concomitant anticoagulant use (Figure 2). Class Ic drugs were more likely to be used than amiodarone and sotalol in women, patients with a history of atrial flutter, patients with AF as their primary diagnosis during the index AF encounter, and patients taking prior or concomitant verapamil or diltiazem.

In the time period after dronedarone was marketed, Class Ic drugs were less likely to be used than amiodarone, sotalol, and dronedarone as patient age increased, in patients with their index AF encounter as an inpatient versus outpatient visit, and in those with prior or concomitant anticoagulant (Figure 3). Class Ic drugs were more likely to be used than amiodarone, sotalol, and dronedarone only in patients with prior or concomitant verapamil or diltiazem.

The median time for follow-up was 409 days (IQR 178, 758) and this differed by drug: 450 days (IQR 203, 801) for Class Ic drugs, 418 days (IQR 173, 770) for amiodarone, 479 days

(IQR 242, 820) for sotalol, and 157 days (IQR 70, 277) for dronedarone. In the 12 months following AAD initiation, the rate of change to a different AAD was 13.1%; this rate varied by the initially prescribed AAD (14.4% for Class Ic, 8.1% for amiodarone, 17.1% for sotalol, and 18.4% for dronedarone; $p<0.001$; Figure 4). Among the 7277 (85%) patients in the study cohort who did not change to another AAD in the 12 months following the initiation of the first AAD, the rate of discontinuation by 12 months was 45.9% and this varied by the initial AAD (40.2% for Class Ic, 51.6% for amiodarone, 39.9% for sotalol, and 69.3% for dronedarone; $p<0.001$; Figure 5).

Discussion

When the decision is made to use an AAD for the management of paroxysmal or persistent AF, selection of the most appropriate AAD should be based upon patient-specific characteristics in order to minimize potential risk from the AAD. Patients without CAD and heart failure have a greater number of guideline-recommended AAD options,^{8–10} yet not all of these options are optimal, given an individual patient's comorbidities and each drug's unique properties. In this study, we provide the first description of AAD use in AF patients <65 years of age without CAD or heart failure in clinical practice. Key study findings include a high use of amiodarone that may be inconsistent with guideline recommendations, rapid adoption of dronedarone, and a very high rate of AAD change and discontinuation in the 1 year following AAD initiation.

During our study period (2006–2010), the prevailing clinical practice guidelines for AF management in the United States recommended flecainide, propafenone, and sotalol as first-line options, and amiodarone and dofetilide as second-line options in patients without CAD, as well as in those with hypertension who did not have substantial left ventricular hypertrophy, regardless of patient age.⁶ Amiodarone was the first-line option for those with hypertension and substantial left ventricular hypertrophy. Subsequent updates in the clinical practice guidelines combined the subgroups with no heart disease and hypertension into one group (no structural heart disease), expanded first-line AAD choices to include dofetilide and dronedarone in patients without structural heart disease, and solidified amiodarone as second-line therapy for AF patients without structural heart disease.^{7,10}

Among patients started on an AAD within 14 days of their first identified AF encounter, the use of Class Ic drugs and amiodarone was nearly identical despite guideline recommendations to reserve amiodarone for second-line therapy for most of these patients (even in 2006–2010). Despite the fact that we were unable to identify patients with asymptomatic left ventricular hypertrophy using claims data, and therefore, were unable to identify those for which amiodarone may have been considered first-line therapy, we expected the proportion of patients who received amiodarone as their first AAD to be far less than the 34%. This extensive use of amiodarone for AF management has been previously reported, but in a broader AF population that primarily included older patients and those with structural heart disease, where amiodarone has been and continues to be considered a first-line option.^{11–16}

There also appeared to be a quick uptake in the use of dronedarone that was very much in contrast to the uptake in dofetilide use following its market release in 2001.¹⁷ Piccinni et al. recently reported on a sharp use uptake in dronedarone in Sweden compared to Italy, but it was noted that dronedarone did not appear to be used preferentially over amiodarone, as some had initially anticipated.¹⁸ In our study, there were a relatively small number of patients receiving dronedarone compared to amiodarone and Class Ic drugs. Furthermore, dronedarone appeared to be selected over Class Ic drugs in patients with similar characteristics to those who received the other Class III drugs, particularly sotalol. Perhaps dronedarone use slowed or declined after our study period, since additional safety concerns about dronedarone were publicized after our study ended in December of 2010.

In addition to clinical practice guideline recommendations, there are other factors that influence AAD drug selection including comorbidities; unique pharmacologic and pharmacokinetic properties of each AAD; and other patient, provider, or regional characteristics. In our study, we found that potentially “sicker” patients, such as those with more comorbidities, prior hospitalizations, more advanced age, or current/past use of anticoagulants, had a greater likelihood of amiodarone or sotalol use over Class Ic drugs. Nevertheless, associations between geographic region and selected AAD likely indicate provider preferences that also played a substantial role in prescribing the specific AAD in this population. Some anticipated associations were observed between AAD properties and AAD selection, such as a lower likelihood of sotalol (which has beta-blocking properties) than Class Ic drugs (no or minimal beta-blocking properties) in patients taking other beta-blockers; however, we did not see a lower likelihood of sotalol (primarily renally cleared) versus Class Ic drugs (not renally cleared) in patients with renal failure. Some of these unexpected associations between AAD and patient characteristics may be due to the lack of a provider’s knowledge about the AAD, the limitations of claims data use, or our inability to account for all of the potential factors contributing to AAD selection in clinical practice. The results of our study raise several questions that merit further investigation, regarding AAD selection in this younger population of AF patients.

Finally, we explored the longitudinal use of each AAD drug. A change in AAD during the 1 year post-initiation was infrequent; however, changes were more common with dronedarone and less common with amiodarone. By contrast, discontinuations of the initial AAD were very common during the 1 year post-initiation, occurring in 46% of patients who did not have a change in AAD during the first year. Discontinuation rates over the first year were nearly identical for Class Ic drugs and sotalol, but the discontinuation rates for dronedarone and amiodarone were very high (69% and 52%, respectively). There are many potential reasons for changes and discontinuations in AAD therapy, including failure to control AF, emerging evidence for safety or effectiveness, non-adherence, and adverse events.^{19–21} Additional research is needed to understand the reasons for these changes and discontinuations, as well as their impact on overall AF management, especially in relation to health care utilization.

Our analysis had several limitations; therefore, our findings should be viewed as hypothesis-generating. First, a prescription claim for an AAD is a very good indicator that the drug was prescribed and picked up by the patient, but a claim does not guarantee that the patient took

the medication. Second, there are other factors associated with drug selection that are not available in this database, such as prescriber experience and preferences, patient personal preferences, or interactions with comorbidities. Third, we used commonly accepted diagnosis and procedure codes to identify the study population and patient comorbidities; however, the use of these claims data are limited. For example, not having a recently-coded claim with a diagnosis for a particular comorbidity could lead to missing eligible patients or missing comorbidities. Finally, it is notable that the study population had private health insurance; therefore, our results may not be applicable to uninsured AF patients of similar age without concomitant structural heart disease.

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Figure 1. Study Cohort

This figure displays the overall study cohort and subsets of patients by time period.

AF, atrial fibrillation

Figure 2. Amiodarone and Sotalol versus Class Ic Drugs (Time Period 1)

This figure displays the factors associated with the use of amiodarone and sotalol versus Class Ic Drugs in time period 1 (before July 1, 2009). Variables remaining in final model but not presented above include: history of rheumatic heart disease, other atrial arrhythmias, thyroid disease, cancer, depression and past/concomitant digoxin use.

BB, beta-blocker; CCB, calcium channel blocker; CI, confidence interval; Dx, diagnosis; Dz, disease; OR, odds ratio

Figure 3. Amiodarone, Sotalol, and Dronedaron versus Class Ic Drugs (Time Period 2)

This figure displays the factors associated with the use of amiodarone, sotalol, and dronedaron versus Class Ic drugs in time period 2 (after June 30, 2009). Variables remaining in final model and not presented above include: history of rheumatic heart disease, other atrial arrhythmias, thyroid disease, cancer, stroke, non-rheumatic valvular heart disease; and prior/concomitant digoxin use.

BB, beta-blocker; CCB, calcium channel blocker; CI, confidence interval; Dx, diagnosis; Dz, disease; OR, odds ratio

Figure 4. Rate of Change to Different AAD in First Year

This figure displays the Kaplan Meier rate of change to different AAD in first year following AAD initiation.

AAD, antiarrhythmic drug

Figure 5. Rate of AAD Discontinuation

This figure displays the Kaplan Meier rate of ADD discontinuation by initial antiarrhythmic drug.

AAD, antiarrhythmic drug

Table 1**Patient Characteristics Overall and by Time Period**

Variable	Overall (n=8562)	Time Period: Before July 2009 (n=5175)	Time Period: After June 2009 (n=3387)
Age, median (IQR) (Years)	56 (49,61)	56 (49,61)	56 (49,60)
Women	2905 (33.9%)	1736 (33.5%)	1169 (34.5%)
Geographic region			
Northeast	755 (8.8%)	451 (8.7%)	304 (9.0%)
North central	2582 (30.2%)	1534 (29.6%)	1048 (30.9%)
South	3815 (44.6%)	2336 (45.1%)	1479 (43.7%)
West	1300 (15.2%)	778 (15.0%)	522 (15.4%)
Unknown	110 (1.3%)	76 (1.5%)	34 (1.0%)
Year of encounter			
2006	783 (9.1%)	783 (15.1%)	-
2007	1459 (17.0%)	1459 (28.2%)	-
2008	1856 (21.7%)	1856 (35.9%)	-
2009	2313 (27.0%)	1077 (20.8%)	1236 (36.5%)
2010	2151 (25.1%)	-	2151 (63.5%)
Index AF encounter			
Hospitalization	5861 (68.5%)	3587 (69.3%)	2274 (67.1%)
Outpatient	2701 (31.5%)	1588 (30.7%)	1113 (32.9%)
AF listed as primary diagnosis	5854 (68.4%)	3539 (68.4%)	2315 (68.3%)
Discharged home to self care	84.6 (n=5861)	84.1 (n=3587)	85.3 (n=2274)
Hospitalization w/in 6 mo. prior to first prescription	668 (7.8%)	420 (8.1%)	248 (7.3%)
Electrical cardioversion during index encounter	1263 (4.8%)	731 (14.1%)	532 (15.7%)
Cardiac ablation during index encounter	109 (1.3%)	67 (1.3%)	42 (1.2%)
History of the following w/in 6 mo. prior to first prescription			
Atrial flutter	1414 (16.5%)	857 (16.6%)	557 (16.4%)
Other atrial arrhythmias	537 (6.3%)	314 (6.1%)	223 (6.6%)
Bradycardia arrhythmias	281 (3.3%)	178 (3.4%)	103 (3.0%)
Pacemaker	96 (1.1%)	61 (1.2%)	35 (1.0%)
Diabetes mellitus	1352 (15.8%)	788 (15.2%)	564 (16.7%)
Hypertension	4426 (51.7%)	2570 (49.7%)	1856 (54.8%)
Rheumatic heart disease*	536 (6.3%)	334 (6.5%)	202 (6.0%)
Non-rheumatic valvular heart disease	1943 (22.7%)	1156 (22.3%)	787 (23.2%)
Renal failure	433 (5.1%)	264 (5.1%)	169 (5.0%)
Liver disease	166 (1.9%)	95 (1.8%)	71 (2.1%)
Thyroid disease	882 (10.3%)	511 (9.9%)	371 (11.0%)
Pulmonary disease	1288 (15.0%)	15.0	514 (15.2%)
Cancer	1190 (13.9%)	731 (14.1%)	459 (13.6%)
Stroke	440 (5.1%)	258 (5.0%)	182 (5.4%)

Variable	Overall (n=8562)	Time Period: Before July 2009 (n=5175)	Time Period: After June 2009 (n=3387)
Cerebral hemorrhage	23 (0.3%)	13 (0.3%)	10 (0.3%)
Depression [†]	514 (6.0%)	52	245 (7.2%)
Obesity [‡]	847 (9.9%)	438 (8.5%)	409 (12.1%)
Bleeding	503 (5.9%)	312 (6.0%)	191 (5.6%)
Rate controlling drug use w/ or w/in 6 mo. of index prescription			
Beta-blocker	4482 (51.9%)	2726 (51.9%)	1756 (51.8%)
Digoxin	1038 (12.1%)	700 (13.5%)	338 (10.0%)
Calcium channel blocker	1484 (17.3%)	900 (17.4%)	584 (17.2%)
Other QT prolonging medication use w/or w/in 6 mo. of index prescription			
Possible	2632 (30.7%)	1654 (32.0%)	978 (28.9%)
Definite	1495 (17.5%)	921 (17.8%)	574 (16.9%)
Anticoagulant use w/ or w/in 6 mo. of index prescription	3718 (43.4%)	2283 (44.1%)	1435 (42.4%)

* Rheumatic heart disease = chronic rheumatic heart disease: ICD-9 codes 393–398 + acute rheumatic fever w/ heart involvement: ICD-9 codes 391.x, 392.0

[†] Depression ICD-9 codes: 296.2, 296.3, 296.5, 300.4, 309.x, 311

[‡] Obesity ICD-9 code: 278.0

AF, atrial fibrillation; IQR, interquartile range; mo., months; w/, with; w/in, within