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Adherence to guideline recommendations for antiarrhythmic drugs in atrial fibrillation

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Abstract

Background—Atrial fibrillation (AF) guideline recommendations for antiarrhythmic drugs (AADs) are based upon the effectiveness and safety of the AAD in patients with selected, concomitant heart disease. It is unknown to what extent these recommendations are being implemented in clinical practice.

Methods—Using commercial health claims, patients with AF were identified and then categorized into mutually exclusive, guideline-established subgroups based upon their most serious concurrent heart disease: heart failure, coronary artery disease (CAD), hypertension, no heart disease. AAD use following the first AF encounter and the identified concurrent heart disease encounter was determined from prescription claims, and this was compared with guideline recommendations.

Results—From January 2006 through December 2010, a total of 331,274 AF patients aged <65 years were identified: 18% heart failure, 23% CAD, 33% hypertension, and 25% no heart disease. Of these, 78,877 (24%) patients filled ≥1 qualifying AAD prescription. The median age was 57 years (interquartile range 52, 61), and 69% were male. A total of 74,191 patients had AADs after both the AF and concurrent heart disease encounters: 27% with heart failure, 25% with CAD, 21% with hypertension, and 19% with no heart disease. In the heart failure and CAD subgroups, 45% and 31% of AADs were inconsistent with first- or second-line guideline recommendations, respectively.

Conclusion—More than one-third of the AADs used in AF patients with CAD or heart failure did not conform to guideline recommendations. This highlights the potential need for increased clinician education and intervention to improve the safe use of AADs for AF management.

Keywords

atrial fibrillation; antiarrhythmic drugs; evidence-based medicine; clinical practice guidelines; adherence

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Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia that affects up to 6.1 million people in the United States, with estimates of AF prevalence increasing to 12 million by 2050.[1,2] One method for maintaining sinus rhythm and reducing recurrence of AF is the use of antiarrhythmic drugs (AADs). These drugs can be harmful if not used appropriately; therefore, clinical practice guidelines were developed to provide specific, evidence-based recommendations to improve the safe and effective use of these drugs. For maintenance of sinus rhythm, AAD selection recommendations are based upon whether a patient has concomitant heart failure, coronary artery disease (CAD), or hypertension because adverse events, especially proarrhythmias, can vary by extent and type of heart disease.[3,4] Little is known about how well these AAD recommendations are incorporated into clinical practice.

The purpose of this study was to determine the frequency of use of different AADs in patients with AF overall and within clinical practice guideline subsets of patients with heart failure, CAD, and hypertension and without heart disease. Conformity to clinical practice guideline recommendations was determined.

Methods

Data source

The Thomas Reuters MarketScan® Commercial Claims and Encounters Database was used to identify the study cohort. This database consists of inpatient, outpatient, and prescription claims data from U.S. employers and health plans for employees and their spouses and dependents. The MarketScan® databases have been used for more than 450 publications of health care utilization and outcomes in a variety of diseases, including atrial fibrillation.[5–7] Data from all patients with an inpatient or outpatient encounter that included a diagnosis of AF (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9] code 427.31) between January 1, 2006 and December 31, 2010 were obtained. The database does not include Medicare claims data, and therefore, does not include patients aged ≥65 years.

Selection of overall study cohort

For this study, only patients with individual-level and pharmacy benefit data were included. The first inpatient or outpatient encounter with a diagnosis of AF was identified and considered the index AF encounter. If the first AF encounter was 30 days before or after a cardiothoracic surgical procedure (ICD-9 codes 35.x to 39.x), then a subsequent AF encounter (if present) was used, provided that it was not within 30 days of another cardiothoracic surgical procedure. Patients aged <30 years at the time of the index AF encounter were excluded due to low incidence of AF in these patients without congenital heart disease; also, patients with ventricular arrhythmias diagnosed at any time were excluded due to use of AADs outside of AF guideline recommendations in these patients (ICD-9 codes 427.1x, 427.41, 427.42, and 427.5x).

Selection of subgroups

Subgroups were determined using the American Heart Association/American College of Cardiology/Heart Rhythm Society clinical practice guidelines in which specific AAD recommendations are based upon the presence of heart failure (regardless of the left ventricular ejection fraction), CAD (with or without prior myocardial infarction), hypertension (with and without substantial left ventricular hypertrophy [LVH]), or none of these.[3] According to the guideline recommendations, for patients with more than one of these coexisting diseases, clinicians should select AADs based upon the most serious

condition (heart failure > CAD > hypertension with LVH > hypertension without LVH).[3] Therefore, in this study, subgroups were identified by first searching for any prior, concomitant, or subsequent inpatient or outpatient encounter with a diagnosis of heart failure (ICD-9 codes 428.xx, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, and 398.91) or cardiomyopathy (ICD-9 codes 425.0, 425.1, 425.2, 425.3, 425.5, 425.7, 425.8, and 425.9).[8] If a patient was ever diagnosed with heart failure, that patient was assigned to the heart failure subgroup. Also, if the date of that diagnosis was *after* the AF index encounter, then it became the subgroup index date. If the diagnosis date was *before* the AF index encounter, then the AF index date was used as the subgroup index date.

For the remaining patients (those without a heart failure diagnosis), the same process was applied for CAD diagnosis (ICD-9 codes 410–414 and 429.2) and then for hypertension diagnosis (ICD-9 codes 402.00, 402.10, 402.90, and any prior hypertension code along with 429.3, 401.x, 403.xx, 404.00, 404.02, 404.10, 404.12, 404.90, 404.92, 405.xx, and 437.2).[8] For patients with hypertension, an attempt was made to differentiate between those with and without left ventricular hypertrophy; however, due to the lack of specific and reliable claims codes for this condition, we could not reliably classify patients into the 2 guideline-recommended subcategories of hypertension.

All remaining patients (those without heart failure, CAD, or hypertension) were classified as not having any of the selected heart diseases, and the AF index encounter date remained their subgroup index date.

Selection of AADs of interest

National Drug Codes (NDCs) for oral formulations of Vaughan Williams Class Ia (quinidine, procainamide, disopyramide), Class Ic (propafenone, flecainide), and Class III (amiodarone, dofetilide, sotalol, and dronedarone) AADs that may be used for the treatment of AF were identified using the 2010 Thomas Reuters RED BOOK®. AAD use was defined by prescription claims for ≥30-day supplies of all selected AADs at any time after the index AF encounter. Prescription claims for ≥30-day supplies of selected AADs at any time after the index dates for heart failure, CAD, hypertension, and no heart disease subgroups were also identified.

Statistical analysis

From the overall study cohort, characteristics of patients taking one or more AADs during the study period were compared with those of patients not taking AADs. Characteristics for comparison included age, sex, geographic region, type of health plan, inpatient versus outpatient index AF encounter, year of AF index encounter, and concomitant atrial flutter. Categorical variables were compared using a chi-square test, and continuous variables were compared using the Wilcoxon rank sum test. The number of different AADs used by each patient during the study period was determined. Trends in use by calendar quarter overall and by age subgroups (patients aged <60 years versus 60–64 years) were determined and were graphically displayed.

From the overall study cohort, the number of patients in each of the 4 subgroups of interest was also determined, and characteristics of these patients were described. The number and proportions of patients taking one or more AADs during the study period were determined for each subgroup. In addition, the number and proportions of AADs used were determined by subgroup. Trends in use by calendar quarter were determined and were graphically displayed. Conformity to guideline recommendations within each subgroup was determined by calculating the proportion of AADs that were used and that were also included as first-line or second-line choices in the guideline recommendations for that subgroup.

Study Funding

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Results

A total of 331,274 patients with an inpatient or outpatient diagnosis of AF met all of the inclusion criteria and none of the exclusion criteria. Of these, a total of 78,877 (24%) patients had a prescription claim for a ≥30-day supply of one or more AADs after their index AF encounter. During the median follow-up of 465 (interquartile range [IQR] 211, 877) days, most patients (86%) received only one AAD, 12% received 2, and 2% received 3 or more. The median time from AF encounter to first prescription claim for an AAD was 29 (IQR 9, 89) days. Overall, the use of Class Ia AADs occurred in only 0.4% of patients. Given the low usage, these drugs were not presented in results, tables, or figures. Of the 78,877 patients identified with an AAD, 71,286 (90%) had ≥1 subsequent AF encounter. Characteristics of patients with and without AADs are presented in Table I. Compared with patients who did not receive AADs, patients who received AADs more often were men, were from the South or North Central United States, were inpatients, and had concomitant atrial flutter.

The proportion of AF patients identified in each calendar year who subsequently received an AAD decreased from 2006 through 2010 (Figure 1). Likewise, the overall number of patients receiving AADs per 10,000 patients with AF per calendar quarter decreased from 2006 through 2010, with sotalol and flecainide use surpassing amiodarone use in 2008 and 2009, respectively (Figure 2A). Trends in AAD use were different among those aged <60 years compared with those aged 60–64 years (Figures 2B and 2C) at their index AF encounter.

After dividing the study population into subgroups based upon inpatient or outpatient diagnoses for comorbidities (heart failure, CAD, hypertension, or none of these) that are specified in clinical practice guidelines to guide AAD selection, a total of 74,191 patients (22%) had an outpatient prescription claim for a ≥30-day supply of one or more AADs after the first subgroup index encounter date. The distribution of patients into these subgroups is shown in Figure 3. Characteristics of patients within each subgroup are presented in Table II.

AF and heart failure

Of the 60,849 patients with atrial fibrillation and heart failure, 16,572 (27%) received a total of 19,043 AADs. Only 55% of the AAD use in this subgroup conformed to guideline recommendations (specifically, 50% of AADs were amiodarone and 5% of AADs were dofetilide). The use of sotalol (19%), dronedarone (9%), propafenone (9%), and flecainide (8%) does not conform to guideline recommendations. AAD use by drug and calendar quarter is shown in Figure 4A.

AF and CAD

Of the 77,782 patients with AF and CAD, 19,062 (25%) received a total of 21,911 AADs. Only 40% of the AAD use conformed to first-line guideline recommendations (27% sotalol, 9% dronedarone, and 4% dofetilide). Amiodarone, a second-line recommendation, accounted for 27% of the AADs used. Propafenone (16%) and flecainide (15%), which are not recommended in patients with CAD, accounted for 31% of the AAD use. AAD use by drug and calendar quarter is shown in Figure 4B. A total of 5070 (27%) of the patients

identified in this subgroup had a myocardial infarction as their qualifying CAD diagnosis for inclusion in the group. Of these, 294 (6%) received propafenone or flecainide.

AF and hypertension

Of the 110,752 patients with AF and hypertension, 23,096 (21%) received a total of 26,106 AADs. Of these patients, only 4.5% had one or more coded claims indicating the presence of LVH. The most frequently used AADs were flecainide (26%), sotalol (22%), propafenone (21%), and amiodarone (18%). All of these high-use AADs are consistent with clinical practice guideline recommendations in the absence of definitive information on the presence of LVH. AAD use by drug and calendar quarter is shown in Figure 4C.

AF without heart failure, CAD, or hypertension

A total of 81,891 patients with AF did not have heart failure, CAD, or hypertension. Of these patients, 15,461 (19%) received 17,326 AADs. The most frequently used drugs were flecainide (33%), propafenone (22%), and sotalol (20%), which are all acceptable according to clinical practice guidelines. A total of 23% of AADs were non–guideline-recommended, first-line AADs (amiodarone in 14% and dofetilide in 3%). AAD use by drug and calendar quarter is shown in Figure 4D.

Discussion

Given the potential risks of AADs, clinical practice guidelines for AF management were developed to provide clinicians with AAD recommendations that minimize the potential risk. However, little is known about AAD use in clinical practice in the United States and whether it conforms to guideline recommendations. In this study, we found that 45% of AAD use in patients with concomitant heart failure and 31% of AAD use in patients with CAD did not conform to first- or second-line guideline recommendations. While this study only provides a snapshot of AAD use based upon claims data, the high rate of nonconformity is concerning. Additional research is needed to better understand the reasons for this lack of conformity to guideline recommendations.

For AF management, much of the recent focus has been on evaluating and comparing a rate- versus rhythm-control strategy, with relatively little attention being given to evaluating or comparing the specific drugs used in those strategies.[9–13] Clinical practice guidelines for AF management provide AAD recommendations based upon concomitant heart disease (heart failure, CAD, or hypertension) because the risks of some AADs may outweigh potential benefits in patients with structural heart disease.[3,4] For example, several AADs, such as Class Ic drugs and dronedarone, can worsen heart failure and/or have been shown to increase the risk of adverse effects or poor outcomes in patients with heart failure.[3,14] Also, Class Ic drugs have been shown to have a higher risk of potentially life-threatening proarrhythmias in patients with CAD and are considered contraindicated in these patients.[15,16] Therefore, there are fewer AAD options for patients with heart failure or CAD.

In applying the guideline recommendations to clinical practice, clinicians are instructed to select an AAD from those recommended for the most severe type of concomitant heart disease that is present (heart failure > CAD > hypertension). For example, a patient with heart failure and hypertension would only be eligible for those AADs recommended for a patient with heart failure. In this study, we applied this hierarchical process and categorized patients by their most severe type of concomitant heart disease to mimic clinical practice. We then looked at the actual AADs that were prescribed and compared them with the recommended AADs for each subgroup. As expected, there was little discrepancy between clinical practice and guideline recommendations in patients with no structural heart disease

because these patients' AAD options are more extensive. It was only within the heart failure and CAD subgroups that we found extensive AAD use that was not recommended by the guidelines.

From the published results of 7 AF registries, 21% to 48% of patients with AF received AADs at enrollment or during the first year after enrollment.[17–25] The types of AADs that were used varied depending upon the years of enrollment and the types of patients with AF that were included. In these studies, little information was found regarding adherence to guideline recommendations in the selection of AADs. One study in Germany reported that <0.2% of patients with left ventricular dysfunction or severe CAD received Class Ic AADs.[22] One study in the United States and Canada reported that use of Class Ic drugs was less likely in patients with heart failure and CAD.[25] One non-US, worldwide study reported that 20% of patients with structural heart disease received Class Ic drugs.[17] In addition, 3 studies were identified that looked at AAD prescription patterns in the United States in the 1990s and 2000s; these studies showed that 10% to 13% of patients with AF received AADs. Drug use in subgroups of patients with other heart diseases was not assessed.[26–28] In one of these studies, Class Ic drugs were the most commonly prescribed AADs in patients who were aged <60 years, indicating that these drugs may be preferred in younger patients with seemingly less concomitant heart disease.[26] Therefore, the results of our study provide the most detailed and contemporary picture of current AAD use in younger AF patients in the United States and have identified several areas of concern that warrant further investigation to improve care.

Our study is also the first to include a snapshot of the use of dronedarone in the United States. Dronedarone was introduced to the market in the third quarter of 2009. We found a substantial uptake in dronedarone use through the end of our study period in all subgroups. Despite being available for <30% of the study period, dronedarone accounted for 9% of all AAD use in patients with heart failure, 9% of AAD use in patients with CAD, 8% of AAD use in patients with hypertension, and 6% of AAD use in patients without any of these selected cardiac diseases. Because our study period ended in November 2010—before increasing reports of dronedarone's safety concerns and publication of the results from the Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS) trial—additional research is needed to determine whether use of dronedarone, including potentially inappropriate use, continues.[29,30]

There are several limitations to this study. This study relies on the use of coded diagnoses during inpatient and outpatient encounters and prescription claims rather than confirmed diagnoses from clinicians or confirmed medication adherence from patients. There may have been mitigating factors not captured by claims data that resulted in the selection of a drug that did not conform to guideline recommendations, including incorrectly coded diagnosis, contraindications to or prior failure of all other AADs, patient preferences, and ambiguity in the guideline recommendations as to the specific definition of heart failure or CAD. Physicians must consider numerous factors in drug selection, and many of those factors were unavailable in this study, which prevented us from assessing potential reasons for selection of drugs that were not recommended by the clinical practice guidelines. Lastly, in patients with hypertension, we were unable to differentiate between those with or without LVH. Guideline-recommended AADs differ between these 2 subgroups, and as such, there may have been patients who received non–guideline-conforming AADs that we were unable to identify.

Conclusion

More than one-third of AF patients with CAD or heart failure received an AAD that did not conform to guideline recommendations. This extensive use of potentially inappropriate AADs highlights the need for more detailed analyses of AAD drug selection, especially in patients with concomitant heart failure and CAD, and the potential need for increased clinician education and intervention to improve the safe use of AAD therapy for AF management.

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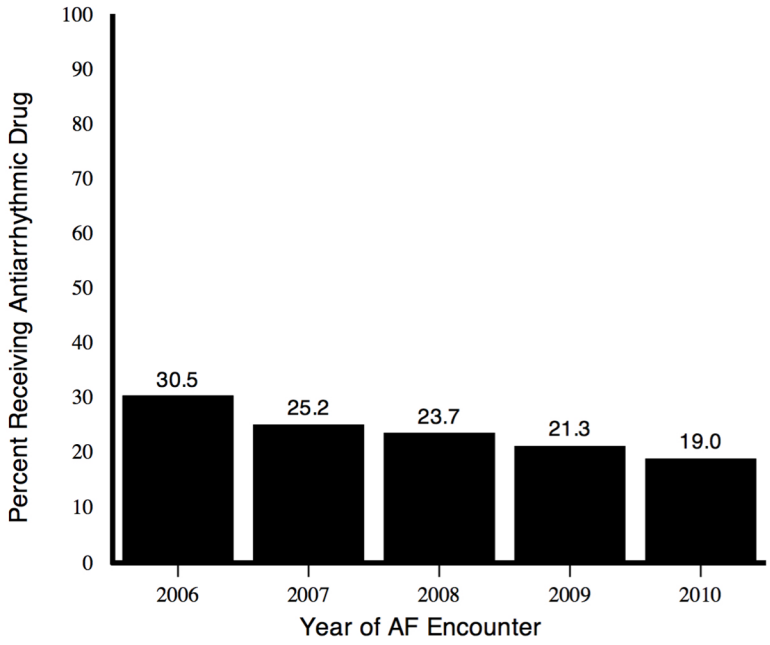

Figure 1. Proportion of patients identified with AF in each calendar year who subsequently received one or more AADs

AAD indicates antiarrhythmic drug; AF, atrial fibrillation.

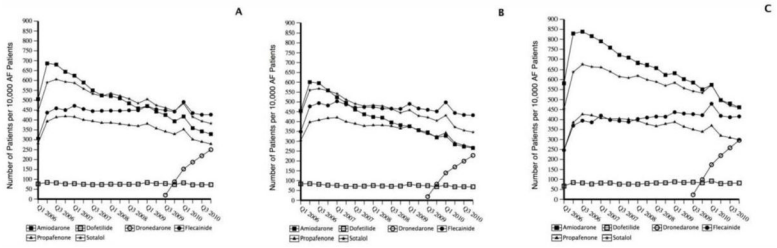

Figure 2. Trends in AAD use in overall AF population and by age subgroups

A. Number of patients taking AADs during each calendar quarter per 10,000 patients with AF diagnosis.

B. Number of patients aged <60 years taking AADs during each calendar quarter per 10,000 patients aged <60 years with AF diagnosis.

C. Number of patients aged 60–64 years taking AADs during each calendar quarter per 10,000 patients aged 60–64 years with AF diagnosis.

AF indicates atrial fibrillation; Q, quarter.

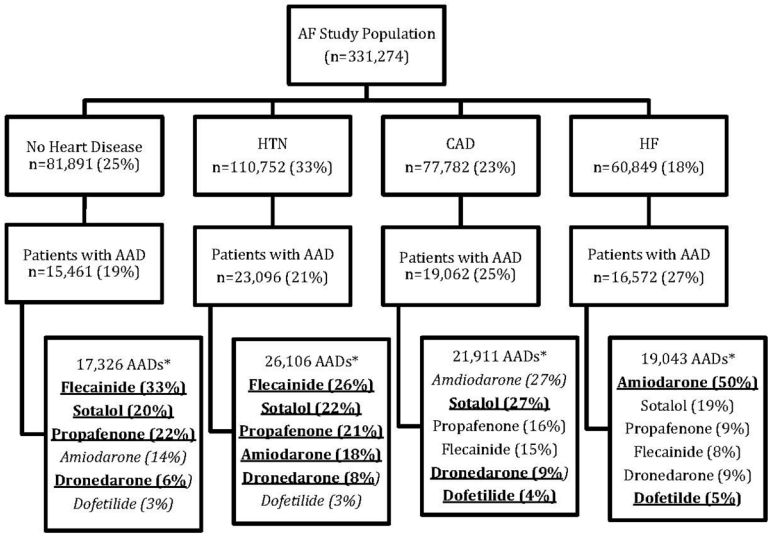

Figure 3. AAD use by guideline-specified subgroups

*Underlined/bolded AAD drugs indicate first-line, guideline-recommended drugs.[4] Italicized AAD drugs indicate second-line, guideline-recommended drugs.[4] Patients could have taken one or more AADs (successively, not simultaneously).

AAD indicates antiarrhythmic drug; AF, atrial fibrillation; CAD, coronary artery disease; HF, heart failure; HTN, hypertension.

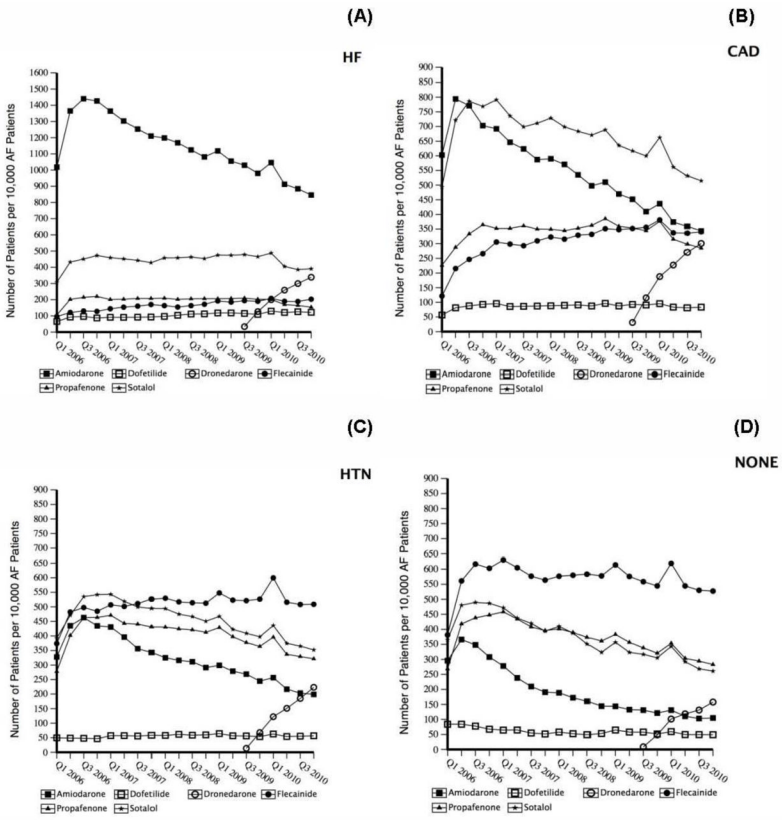

Figure 4. Number of patients taking AADs per 10,000 AF patients with coexisting disease

AAD indicates antiarrhythmic drug; AF, atrial fibrillation; CAD, coronary artery disease; HF, heart failure; HTN, hypertension; Q, quarter; NONE, none of the specified heart diseases.

Table I

Characteristics of the Overall Population

Characteristic	No AAD (n=252,397)	AAD (n=78,877)	P-value
Age, yrs, median (IQR)	56 (50, 61)	57 (52, 61)	<0.001
Sex			<0.001
Male	156,838 (62)	54,547(69)	
Female	95,559 (38)	24,330 (31)	
Region			<0.001
Northeast	43,981 (17)	8984 (11)	
North Central	70,589 (28)	23,934 (30)	
South	94,558 (38)	32,440 (41)	
West	39,216 (16)	12,221 (16)	
Unknown	4053 (2)	1298 (2)	
Type of health plan			<0.001
HMO	40,348 (17)	11,835 (15)	
PPO	157,824 (64)	50,359 (66)	
POS	20,731 (9)	6917 (9)	
Other	26,188 (11)	7810 (10)	
Index AF encounter			<0.001
Inpatient	43,061 (17)	15,874 (20)	
Outpatient	209,336 (83)	63,003 (80)	
Year of index AF encounter			<0.001
2006	45,918 (18)	20,147 (26)	
2007	35,844 (14)	12,103 (15)	
2008	59,738 (24)	18,573 (24)	
2009	57,233 (23)	15,488 (20)	
2010	53,664 (21)	12,566 (16)	
Atrial flutter before/during index AF encounter	7557 (3)	4723 (6)	<0.001

Data are presented as n (%) unless otherwise specified.

AAD indicates antiarrhythmic drug; AF, atrial fibrillation; HMO, health maintenance organization; IQR, interquartile range; POS, point of service; PPO, preferred provider organization.

Table II

Characteristics of Patients Receiving AADs within Subgroups

Characteristic	Heart Failure (n=16,572)	CAD (n=19,062)	Hypertension (n=23,096)	No Heart Disease (n=15,461)
Age, yrs, median (IQR)	58 (53, 62)	59 (54, 62)	57 (52, 61)	55 (47, 60)
Sex				
Male	11,391 (69)	14,096 (74)	15,172 (66)	10,579 (68)
Female	5181 (31)	4966 (26)	7924 (34)	4882 (32)
Region				
Northeast	1775 (11)	2280 (12)	2553 (11)	1805 (12)
North Central	5091 (31)	5868 (31)	6973 (30)	4672 (30)
South	7073 (43)	8293 (44)	9518 (1)	5690 (37)
West	2373 (14)	2356 (12)	3663 (16)	3068 (20)
Unknown	260 (2)	265 (1)	389 (2)	226 (2)
Type of health plan				
HMO	2443 (15)	2593 (14)	3404 (15)	2536 (17)
PPO	10,647 (66)	12,368 (67)	14,944 (66)	9662 (64)
POS	1393 (9)	1679 (9)	1987 (9)	1362 (9)
Other	1704 (11)	1968 (11)	2177 (10)	1485 (10)
Index AF encounter				
Inpatient	5980 (36)	4070 (21)	4113 (18)	1917 (12)
Outpatient	10,592 (64)	14,992 (79)	18,983 (82)	13,544 (88)
Year of index AF encounter				
2006	2576 (16)	3398 (18)	3792 (16)	3920 (25)
2007	2652 (16)	3170 (17)	3657 (16)	2151 (14)
2008	3831 (23)	4363 (23)	5434 (24)	3510 (23)
2009	4134 (25)	4467 (23)	5418 (24)	2963 (19)
2010	3379 (20)	3664 (19)	4795 (21)	2917 (19)
Time from index date to first AAD prescription fill, median number of days (IQR)	25 (8, 71)	25 (8, 69)	26 (8, 74)	26 (8, 72)
Proportion of days with any AAD following index date, median (IQR)	53% (18, 96)	64% (20, 99)	71% (24, 100)	67% (21, 99)
Proportion of days with initial AAD following index date, median (IQR)	47% (16 94)	57% (17, 98)	64% (20, 99)	61% (18 99)
Prior prescription for the initial AAD	7293 (44)	9404 (49)	10,748 (47)	6164 (40)

Data are presented as n (%) unless otherwise specified.

AAD indicates antiarrhythmic drug; AF, atrial fibrillation; CAD, coronary artery disease; HMO, health maintenance organization; IQR, interquartile range; POS, point of service; PPO, preferred provider organization.