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ORIGINAL RESEARCH

US Antiarrhythmic Drug Treatment for Patients With Atrial Fibrillation: An Insurance Claims—Based Report

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BACKGROUND: Current American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines and European Society of Cardiology guidelines recommend antiarrhythmic drugs (AADs) for maintenance of sinus rhythm in patients with atrial fibrillation. We assessed the concordance between healthcare provider real-world practice and current guidelines with respect to first-line AAD rhythm management.

METHODS AND RESULTS: Administrative claims data from the deidentified Optum Clinformatics Data Mart database were used. Patients were included if they were initiated on an AAD in 2015 to 2016, had 1 year of continuous data availability before their first AAD pharmacy claim, and had a diagnosis for atrial fibrillation within that period. Concordance was assessed by comparing the AAD initiated by the healthcare provider against guideline recommendations for first-line treatment, given the presence of heart failure, coronary artery disease, both, or neither (as determined by *International Classification of Diseases, Ninth Revision* and *Tenth Revision* [ICD-9 and ICD-10] codes). Concordance was also assessed by provider type using Medicare taxonomy codes. For the 15 445 patients included, 51% of healthcare providers initiated AAD treatments with amiodarone, 18% flecainide, 15% sotalol, 8% dronedarone, 5% propafenone, and 2% dofetilide. The overall rate of guideline concordance was 61%, with differences by provider type: 67% for electrophysiologists, 61% for cardiologists, and 60% for others (internal medicine, etc).

CONCLUSIONS: There continues to be a sizable gap in concordance between practice and guidelines in first-line rhythm management of patients with atrial fibrillation. Further research is needed to identify possible explanations for non–guideline-recommended use of AADs, in addition to enhanced AAD educational strategies for practitioners.

Key Words: antiarrhythmic drug ■ atrial fibrillation ■ guideline adherence

trial fibrillation (AF) is a cardiac arrhythmia that affects up to 6.1 million people in the United States, and is associated with reduced quality of life and increased risk of stroke and mortality.¹⁻⁴ Rhythm control strategies can be used to maintain sinus rhythm, including cardioversion, optimization of clinical factors (sleep apnea, hypertension, alcohol intake, body weight), antiarrhythmic drugs (AADs), and catheter-based ablation in patients with paroxysmal or persistent AF.^{1,2,5} Patients with comorbid conditions such as coronary artery disease (CAD) or congestive heart failure have increased risks for adverse events

related to AADs, including serious events like ventricular pro-arrhythmia.^{6,7}

Clinical trials evaluating rhythm management modalities have shown varying degrees of success in different patient populations, including identification of serious adverse outcomes and increased mortality. Based on this body of evidence, the American Heart Association/American College of Cardiology/Heart Rhythm Society developed guideline recommendations for rhythm control with specific AADs as first-line therapy for patients, and selection based on specific patient characteristics and comorbidities (Figure 1). 1.2

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CLINICAL PERSPECTIVE

What Is New?

- Guideline concordance is still an important consideration in contemporary antiarrhythmic drug treatment to maintain sinus rhythm for patients with atrial fibrillation.
- Low concordance may be exposing patients to unnecessary risks of serious adverse events associated with specific antiarrhythmic drugs.

What Are the Clinical Implications?

- These findings highlight the need for further education and understanding by healthcare practitioners around guideline recommendations for antiarrhythmic drug use in treating patients with atrial fibrillation.
- There is a need for further research into understanding reasons for discordance from the current maintenance of sinus rhythm algorithm and to educate on and raise awareness of the importance of guideline adherence for healthcare practitioners.

Nonstandard Abbreviations and Acronyms

AAD antiarrhythmic drug

CAST Cardiac Arrhythmia Suppression Trial

HCP healthcare provider

Despite clear recommendations on selection of AADs for specific patient types, intended to maximize success and mitigate risks, several analyses have suggested that real-world guideline concordance is low.8-12 Given the significant and growing magnitude of the public health burden of AF,13 as well as the inherent need for treatment optimization in this patient population, a further examination to assess the direction of this trend is warranted. Larger-scale studies evaluating contemporary treatment with AADs and guideline concordance, particularly in light of the most recent published guidelines,² are lacking. Therefore, using a large national administrative claims data set representing a more recent patient population and medical practice under current American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines, we sought to assess the current levels of prescriber concordance against earlier observations.

METHODS

Patient-level data from the deidentified Optum Clinformatics Data Mart database, comprising pharmacy and medical claims information, demographic data, and administrative data for >60 million individuals, were used. The analytical methods and study materials that support the findings of this study are available from the corresponding author upon reasonable request. One of the authors (C.J.R.) has full access to the data and takes responsibility for its integrity and the data analysis. All authors had the ability to review the data throughout the conduct of the study. This study was exempt from obtaining institutional review board approval and informed patient consent because it constitutes research of anonymized data.

Cohort Selection

The date of first pharmacy claim for amiodarone, dofetilide, dronedarone, flecainide, propafenone, or sotalol in 2015 or 2016 was defined as the index date. Patients meeting the following criteria were included in the analysis (Figure 2): continuous enrollment in the database for 1 year before the index date (the "baseline period"); age ≥18 years at the index date; AF diagnosis based on International Classification of Diseases, Ninth Revision and Tenth Revision (ICD-9 and ICD-10) codes during the baseline period; no AAD claim in the baseline period; index AAD prescription from a provider with a valid National Provider Identifier and identification number: and refill AAD claim from the same provider following the index prescription claim. CAD diagnosis was defined using ICD-9 and ICD-10 codes designating atherosclerosis in coronary arteries, past history of myocardial infarction or unstable angina with hospitalization, or history of a coronary revascularization procedure. Patients were excluded from the analysis if the first AAD prescription was by providers with nurse practitioner, physician's assistant, or student/trainee taxonomy codes (code starting in "363" or code 390200000X).

Statistical Analysis

Demographic, clinical, and treatment characteristics were summarized descriptively. Comorbidities, including those used in the tabulation of CHA₂DS₂-VASc scores (score on risk factors of congestive heart failure, hypertension, age ≥75 years, age 65–74 years, diabetes mellitus, stroke/transient ischemic attack/thromboembolism, vascular disease, female sex), were determined using *ICD-9*, *ICD-10*, Current Procedural Terminology, and Healthcare Common Procedure Coding System diagnosis and procedure codes in the baseline period.

Concordance was assessed by comparison of actual treatment versus recommendations from the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines on AF, which were unchanged in the 2019 update with respect to AADs (Figure 1). These guidelines focus on CAD and heart failure (HF) in delineating structural heart disease and the appropriate use of AADs. Thus,

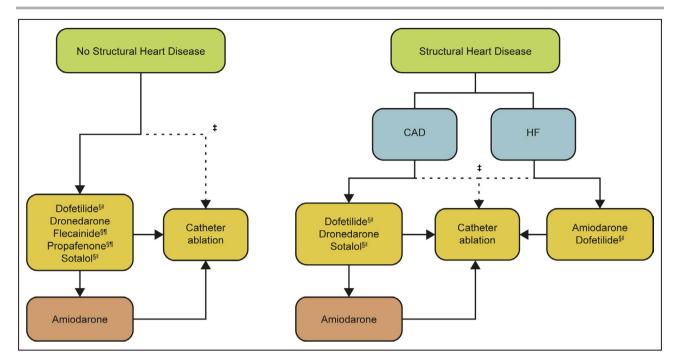


Figure 1. Guideline recommendations for AAD use in patients with AF.

AAD indicates antiarrhythmic drug; AF, atrial fibrillation; CAD, coronary artery disease; HF, heart failure; and LVH, left ventricular hypertrophy. Catheter ablation is only recommended as first-line therapy for patients with paroxysmal AF (Class IIa recommendation). Drugs are listed alphabetically. †Depending on patient preference when performed in experienced centers. §Not recommended with severe LVH (wall thickness >1.5 cm). Should be used with caution in patients at risk for torsades de pointes ventricular tachycardia. Should be combined with atrioventricular nodal blocking agents. Reprinted from January et al¹ with permission. Copyright © 2014, Elsevier.

concordance was calculated by tabulating the percentage of patients treated as recommended in the guidelines based on each patient's comorbidities (specifically whether they had only CAD, only HF, both CAD and HF, or neither CAD nor HF). In patients with CAD and HF, amiodarone was considered as an acceptable option in the primary analysis.

Concordance was also evaluated by the type of provider (electrophysiologist, cardiologist, or other, which included all other provider types) prescribing the AAD using Centers for Medicare & Medicaid Services Healthcare Provider Taxonomy codes. AAD refills had to be prescribed by the original prescriber to be included in the type of provider analysis. Chi-squared tests were used to assess differences in concordance between provider types. Concordance was also tabulated by treatment initiation year (2015 or 2016). Overall concordance was calculated as a weighted average of concordance rates across provider types.

RESULTS

Patient Demographics and Clinical Characteristics

Of 146 737 patients with an AAD pharmacy claim in 2015 to 2016, 15 445 met all inclusion and exclusion

criteria (Figure 2). Over half (51%) were initiated on amiodarone, followed by 18% on flecainide, 15% on sotalol, 8% on dronedarone, and the remaining patients on propafenone (6%) and dofetilide (2%; Table 1).

Demographics, clinical comorbidities, and concomitant medications are provided in Table 1. Those treated with dofetilide had the highest proportion of patients prescribed an anticoagulant (68%), and those treated with amiodarone had the lowest proportion of patients prescribed an anticoagulant (38%). The most common comorbidity across all AADs was hypertension, followed by CAD and valvular disease. Comorbidities were most frequent in patients initiated on amiodarone, apart from valvular heart disease, which was most frequent in patients initiated on dofetilide. Similarly, patients initiated on amiodarone had the highest CHA₂DS₂-VASc score, with 80% reporting a score of ≥4 compared with 63% of patients initiated on dofetilide, 55% on dronedarone, 44% on propafenone, 44% on sotalol, and 39% on flecainide (Table 1).

About one-fifth (18%) of patients in this cohort were prescribed their first AAD by an electrophysiologist, 52% by a cardiologist, and 30% by a prescriber of type "other" (Table 2). Of the "other" group, 69.3% had a taxonomy code designating internal medicine, hospitalist, family medicine, or geriatrics, and 12.1% had

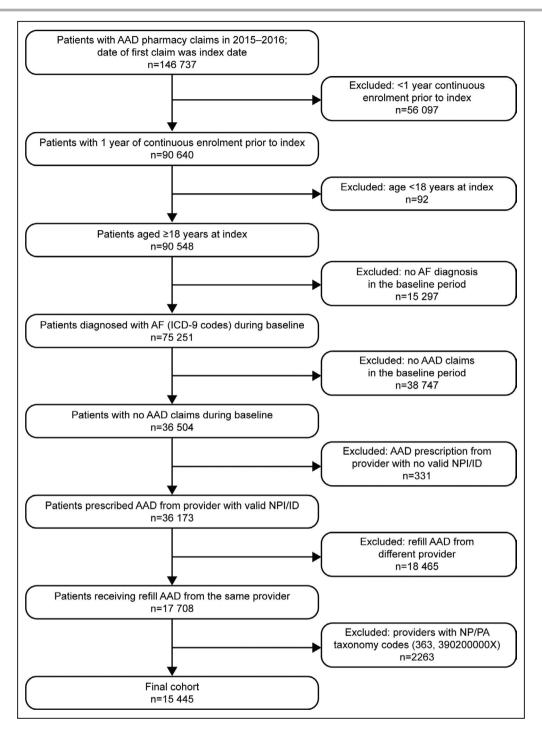


Figure 2. Patient attrition.

AAD indicates antiarrhythmic drug; AF, atrial fibrillation; *ICD-9*; *International Classification of Diseases*, *Ninth Revision*; NP/PA, Nurse Practitioner/Physician Assistant; and NPI/ID, National Provider Identifier/identification number.

no taxonomy code data available. Across all patient cohorts, healthcare providers (HCPs) in the "other" category tended to prescribe amiodarone at a rate substantially above all other agents; cardiologists tended to use amiodarone as well as more class IC agents (ie, flecainide, propafenone) compared with other agents.

Electrophysiologists, however, were more diversified with respect to AAD usage (Table 2).

Guideline Concordance

Overall guideline concordance was 61%, with the rate being lowest in patients with CAD only (31%)

Table 1. Patient Demographics and Clinical and Treatment Characteristics

Characteristic	Amiodarone (n=7931; 51.3%)	Dofetilide (n=347; 2.2%)	Dronedarone (n=1203; 7.8%)	Flecainide (n=2814; 18.2%)	Propafenone (n=849; 5.5%)	Sotalol (n=2301; 15.0%)	Total (n=15 445)
Demographic characteristics							
Age, y, mean (SD)	74.9 (9.9)	68.7 (10.0)	69.6 (11.0)	66.6 (11.6)	67.2 (11.9)	70.7 (10.7)	71.8 (11.1)
Male sex, %	57	63	54	50	53	57	55
Clinical characteristics, %	<u>'</u>						
Coronary artery disease	72	64	54	34	38	62	60
History of ischemic stroke*	14	7	8	6	7	11	11
Peripheral artery disease [†]	41	24	26	17	19	27	32
Diabetes mellitus	41	37	31	22	22	32	34
Heart failure	56	50	21	11	13	31	39
Hypertension	94	92	87	79	84	90	89
Venous thromboembolism	5	2	3	2	2	3	4
CKD stage I-III	21	12	11	7	9	13	16
CKD stage IV-V	7	1	2	1	1	2	4
Cardiomegaly	31	27	18	14	14	21	25
Valvular disease	52	55	44	33	32	43	45
CHA ₂ DS ₂ -VASc score, %							
0–1	3	7	11	22	20	20	8
2–3	18	30	35	40	36	36	31
4–5	46	45	41	31	36	36	43
6+	34	18	14	8	8	8	18
Concomitant medications, %						,	
Anticoagulants	38	68	52	41	40	43	41
Direct oral anticoagulants	20	47	37	31	28	26	25
Warfarin	18	21	15	10	11	16	16
Rate control	67	81	74	70	64	66	68
Beta blockers	59	72	62	55	52	57	58
Nondihydropyridine CCB	14	18	20	22	20	16	17
Digoxin	9	11	7	4	5	8	7
P2Y ₁₂ inhibitors	11	8	7	1	4	8	8

CCB indicates calcium channel blocker; CHA_2DS_2 -VASc score, score on risk factors of congestive heart failure, hypertension, age \geq 75 years, age 65–74 years, diabetes mellitus, stroke/transient ischemic attack/thromboembolism, vascular disease, female sex; and CKD, chronic kidney disease.

†Includes coronary artery disease (evidence of atherosclerosis in coronary arteries, past history of myocardial infarction or unstable angina with hospitalization, or history of coronary revascularization procedure) and peripheral artery disease (evidence of atherosclerosis in peripheral arteries or evidence of revascularization procedure of peripheral arteries).

and highest in patients with CAD and HF (79%). Concordance was significantly different (*P*<0.0001) across provider groups: 67% for electrophysiologists, 60% for cardiologists, and 61% for other prescribers (Table 3).

Rates of concordance by HCPs for patients initiating therapy between 2015 (61%) and 2016 (62%) were relatively unchanged (Table 4).

DISCUSSION

The present analysis suggests that there is at least some level of suboptimal guideline concordance for patients with and without structural heart disease (CAD/HF or no CAD/HF, respectively). This outcome appears to be driven by very high use of amiodarone in first-line settings as well as the use of class IC agents (flecainide, propafenone) in patients with CAD.

The EAST-AFNET 4 (Early Treatment of Atrial Fibrillation for Stroke Prevention) trial supports first-line use of AADs for managing AF.¹⁵ Still, it is acknowledged that guidelines for the maintenance of sinus rhythm are based on Level of Evidence C, which obliges the clinician to be flexible in practice regarding both safety and efficacy considerations from variable levels of evidence. For example, in the pivotal AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) First

^{*}Includes only ischemic stroke (but not transient ischemic attack).

Table 2. First-Line AAD Use in AF by Provider Type Among Patients With CAD and Not HF (CAD Only), HF and Not CAD (HF Only), Both CAD and HF (CAD and HF), and Without CAD and HF (No CAD or HF)

	Cardiologist	Electrophysiologist	Other*	Total 4650	
n	2576	796	1278		
CAD only, %					
Amiodarone	43	27	65	47	
Dofetilide [†]	1	6	1	2	
Dronedarone [†]	11	12	7	10	
Flecainide	18	28	8	17	
Propafenone	6	6	4	6	
Sotalol [†]	20	22	15	19	
n	602	205	490	1297	
HF only, %			<u> </u>		
Amiodarone [†]	59	49	77	64	
Dofetilide [†]	2	10	2	3	
Dronedarone	6	5	4	5	
Flecainide	13	17	4	10	
Propafenone	5	3	2	4	
Sotalol	14	16	11	13	
n	2071	630	1968	4669	
CAD and HF, %					
Amiodarone	74	58	85	77	
Dofetilide [†]	2	13	1	3	
Dronedarone	5	6	2	4	
Flecainide	5	6	2	4	
Propafenone	2	1	1	1	
Sotalol	13	16	9	12	
n	2725	1150	954	4829	
No CAD or HF, %					
Amiodarone	27	14	48	28	
Dofetilide [†]	1	3	1	2	
Dronedarone [†]	11	9	8	10	
Flecainide [†]	36	50	18	36	
Propafenone [†]	11	10	7	10	
Sotalol [†]	14	13	17	14	

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

Antiarrythmic Drug Substudy,¹⁶ amiodarone was found to be more effective at maintaining sinus rhythm than both sotalol and class I AADs, but the study did not assess effectiveness versus dofetilide or dronedarone. Serious adverse drug effects were uncommon within the 1-year time frame of the primary end point of the AFFIRM substudy, although adverse effects that led to discontinuation of a drug were frequent. Amiodarone is associated with risk of complications (including cardiovascular and extracardiac adverse events such as pulmonary and liver toxicity), hyper- and hypothyroidism, photosensitivity, neuropathy, blindness, and a blue

discoloration of the skin.^{10,17} Amiodarone initiation also requires loading, monitoring of respiratory functions, and repeated laboratory tests, adding to patient and healthcare system burden. In our analysis, amiodarone was the most used AAD in first-line treatment despite guideline recommendations for other agents for most patients with AF. Alongside anticoagulation for stroke prevention and rate control considerations, this is consistent with findings indicating the persistence of this practice during the past 2 decades.^{8–12} An explanation for this observation and lower use of other AADs includes the legacy of the treatment¹⁸ coupled with

^{*}Other is defined as any medical category that does not fit within the predesignated groups.

[†]First-line option in the Heart Rhythm Society/American College of Cardiology/American Heart Association 2014 guidelines.

Table 3. Concordance to 2014 AHA/ACC/HRS Guidelines for Rhythm Management in AF by Provider Type*

%	Cardiologist	ardiologist Electrophysiologist		Total
CAD only	32	40	23	31
HF only	61	59	78	67
CAD and HF	76	71	86	79
No CAD or HF	73	86	52	72
All patients	60	67	61	61

ACC indicates American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association; CAD, coronary artery disease; HF, heart failure; and HRS, Heart Rhythm Society.

*Concordance was significantly different by provider type (χ^2 =8.765; P<0.0001).

amiodarone's strong antiarrhythmic effects, specific risks associated with dofetilide and sotalol use, and potential cost considerations. ^{5,19} Thus, patients treated with amiodarone in real-world practice may reflect considerations of costs and time for drug loading even if resulting in an AAD recommendation outside the guidelines.

The use of class IC agents (flecainide/propafenone) in patients with CAD observed in our study also raises some concerns. In the post-myocardial infarction population, IC agents have been associated with increased risk of deaths attributable to proarrhythmia, based on evidence from CAST (Cardiac Arrhythmia Suppression Trial), a multicenter, doubleblind, randomized, controlled trial.⁶ Considering that CAST included patients who were up to 2 years post-myocardial infarction, AF guidelines do not recommend use of IC agents in individuals with CAD or structural heart disease. Recent studies and analyses of IC agents, including cardioversion and "pill-in-thepocket" efficacy with flecainide, 20 have broadened the appeal of these agents. Furthermore, contemporary reviews have challenged restrictions of IC agents in all individuals with CAD such as those who have not had a prior myocardial infarction or who exhibit ischemia on stress testing.21 These elements, in addition to the remoteness of CAST (nearly 30 years after publication), may explain the considerable use of IC agents in CAD. Potential coding of CAD in the presence of nonobstructive disease as evidenced on imaging modalities, or setting of demand ischemia, may also contribute to this discordance, a limitation inherent to *ICD-9*– and *ICD-10*–based review.

Our analysis also found that there was differing concordance by provider type, with "other" HCPs showing the lowest concordance, followed by cardiologists and then electrophysiologists; these rates are comparable with previously published studies.8 The prescribing behavior of the specialist HCPs may be attributable to the greater knowledge about treatment options and guidelines, as well as potential comfort levels in using different AADs among electrophysiologists and cardiologists.8 However, one caveat in interpreting our findings is the volume of use of AADs by HCP type, as well as the AADs that are used by these specialty HCPs. Clearly, the high and nearly exclusive use of amiodarone by other HCPs results in this group's high guideline concordance with respect to HF. Electrophysiologists are most diversified with respect to AAD treatments used in practice, and general cardiologists are intermediate (with greater use of class IC agents and sotalol) regarding AAD treatments used. Additionally, the lower use of dofetilide by the general cardiology and "other" HCPs may be explained by restrictions on its use (ie, Risk Evaluation and Mitigation Strategies program limited prescribing to specialty cardiologists) during the period of this study.²²

Knowledge gaps and clinical bias among providers, particularly for other (noncardiology specialty) HCPs, might also account for some of the discordance between actual practice and AAD guidelines; these may be driven by the overall paradigm of rhythm management, which has largely shifted in the past 10 years. For example, there is currently increased emphasis being placed on anticoagulation, ²³ particularly direct oral anticoagulants.⁸ In addition, the relative incidence of complications related to real-world AAD prescribing, versus other components of management of AF such as anticoagulation, make it difficult to power a difference in outcomes in the observational research to instill recommended use.^{8,24}

Finally, although it is a class IIa recommendation as a first-line choice (and class I after >1 AAD in select

Table 4. Guideline Concordance in Patients Initiating in 2015 and 2016

	2015 Initiation			2016 Initiation				
%	Cardiologist	Electrophysiologist	Other	Total	Cardiologist	Electrophysiologist	Other	Total
CAD only	32	40	23	31	33	39	23	32
HF only	61	60	76	67	61	58	80	68
CAD and HF	76	72	86	80	75	69	87	79
No CAD or HF	73	87	51	72	73	84	52	72
All patients	59	68	61	61	60	66	61	62

CAD indicates coronary artery disease; HF, heart failure.

patients), there is also growing interest around catheter ablation as a first-line approach.²⁵ In patients following an "ablation first" treatment paradigm, post-ablation first AAD selection may favor better efficacy in maintaining sinus rhythm over a long-term safety profile if only short-term dosing is expected.

Examples of low concordance between practice and guidelines are also numerous in other areas of cardiology^{23,26-28}; as such, a variety of methods, from financial incentives²⁹ to tools and system redesign strategies for increasing adherence to guidelines, have been introduced in the United States. One example is the American Heart Association's Get With The Guidelines initiative, a quality improvement registry designed to improve adherence to AF guidelines.³⁰⁻³⁴ Outcomes of the initiative related to AAD use are still to be made available.

Currently, in the United States up to 6.1 million individuals have a diagnosis of AF, and the number of patients with AF is expected to double during the next 25 years, 1-4 proportionately adding to the clinical burden of managing this condition among specialty HCPs as well as noncardiology HCPs. With the rates of discordance in AAD guideline prescribing appearing to continue, we underscore the implications from previous studies such as risk for serious adverse events including ventricular arrhythmias and death.8-12 Further research revealing possible explanations of the low levels of guideline adherence and educational strategies (eg, safety considerations in the choice of AADs),^{1,2} prescribing tools, or structural changes to address the discordance are needed. Prescribing behaviors may change based on the recently released European Society of Cardiology 2020 guidelines on the diagnosis and treatment of AF, which downgraded sotalol in certain patients, included ablation as a first-line rhythm control treatment consideration, and recommended amiodarone be considered after other AADs.⁵ The revised European Society of Cardiology guidelines also presented the ABC treatment pathway that promotes integrated care of patients with AF on the basis of patient attributes: (A) avoiding stroke, (B) better symptom control, and (C) managing comorbidities.

Study Limitations

Because of the limited specificity of certain *ICD-9* and *ICD-10* codes and potential lack of codes for some relevant clinical attributes, there is a risk that the complete patient profile cannot be fully discerned from administrative claims. For example, as data on heart failure severity (eg, New York Heart Association classification) were not readily available, it was not possible to assess if administration of dronedarone was for patients in the New York Heart Association class IV category, 35,36 a

contraindicated population. Furthermore, other potential indications for AADs that could have impacted treatment choice (eq. ventricular tachycardia) were not examined. Similarly, in real-world practice, an initially selected AAD may be chosen, with plans to switch to medications in line with guideline recommendations a short time later. However, potentially missing and relevant clinical conditions are unlikely to have greatly altered the magnitude of our findings. AAD switching was not evaluated, so some patients treated initially with one AAD may have then been treated with a different ADD for long-term AF management in line with guidelines. Finally, the older populations represented within the current data set are likely to have had more comorbidities (ie, chronic obstructive pulmonary disease/asthma) and diseases resulting in shorter life expectation, such as cancer, than younger populations, which may in turn have affected treatment choices. This may be partly driven by the data source, which represented a commercially and Medicare Advantageinsured population in the United States and may not be representative of other types of patients, namely, those who are uninsured or on Medicaid. Despite these limitations, this cohort is the largest and most up-to-date evidence on guideline concordance.

CONCLUSIONS

This analysis of a large national data set indicates that a considerable gap in concordance between clinical practice and AAD guidelines may continue to persist across provider types in the United States, and suggests the need for increased provider education to optimize AF management. Further research revealing possible explanations for the lack of guideline adherence and educational strategies, prescribing tools, or structural changes to address the discordance are critically needed, particularly given the growing prevalence of AF within the aging population.

ARTICLE INFORMATION

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Disclosures

Drs Kim and Tardos are research consultants to Sanofi. Dr Ronk is an employee of Sanofi. Drs Koren and Patel are former employees of Sanofi.

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