

Use of Chronic Medications Among Patients with Non-Valvular Atrial Fibrillation

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Abstract

Background Frequency of administration (once daily versus more than once daily) is believed to be an important consideration affecting drug choice.

Objective The aim of this study was to describe the characteristics of patients with non-valvular atrial fibrillation (NVAF) and the extent to which they take chronic medications, other than anticoagulants, more frequently than once daily.

Methods Using data from a large, national database of health insurance claims, patients with a diagnosis of

NVAF between 1 July 2008 and 30 September 2011 were identified, along with their prescription medications, to determine the proportion of patients taking chronic medications more than once a day. Prescription medications, co-morbidities, and CHADS₂ and CHA₂DS₂-VASc scores were evaluated. CHADS₂ assesses the risk of stroke in NVAF patients with the following risk factors: Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, and history of prior Stroke or transient ischemic attack. The CHA₂DS₂-VASc score adds the following risk factors to the CHADS₂ score: Age 65–74 years, Vascular Disease, and Sex Category (Female).

Results Overall, 324,172 patients with NVAF with mean CHADS₂ and CHA₂DS₂-VASc scores of 1.51 and 3.08, respectively, were included in the study. Of these patients, 299,716 (92.5 %) took chronic medications, with an average of 6.9 medications per patient, and 215,527 (66.5 % of all patients or 71.9 % of those taking chronic medications) took medications more than once per day.

Conclusion Use of chronic medications other than anticoagulants is common among patients with NVAF, and medications are typically taken multiple times per day. The average number of medications per patient and multiple therapeutic classes prescribed underscore the clinical complexity of NVAF patients. Hence, the choice of a once daily anticoagulant versus a more than once-daily anticoagulant may be less relevant in a real world NVAF population in terms of a potential convenience benefit.

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Key Points

This study examines the extent to which patients with non-valvular atrial fibrillation (NVAF) take a variety of different chronic medications other than oral anticoagulants more than once a day.

Of the 324,172 patients with NVAF included in the study, 92.5 % were prescribed chronic medications other than oral anticoagulants, and 66.5 % were identified as taking these medications more than once per day. Among patients who were prescribed chronic medications, 71.9 % were identified as taking their medications more than once per day.

Among the NVAF patients who took chronic medications, the mean number of medications taken was 6.9 and the median was 6. The mean number of therapeutic classes was 6.4 and the median was 6.

The average number of medications per patient and multiple therapeutic classes prescribed underscore the clinical complexity of NVAF patients.

Almost half (46.8 %) of our sample of NVAF patients with CHADS₂ ≥ 1 received no oral anticoagulant treatment.

1 Introduction

1.1 Atrial Fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia and strongest independent risk factor for stroke [1, 2]. Non-valvular atrial fibrillation (NVAF), which comprises the majority of AF [3], is defined as a rhythm disturbance occurring in the absence of rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair [1]. CHADS₂ is a commonly used risk stratification scheme for assessing the risk of stroke in NVAF patients with the following risk factors: Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, and history of prior Stroke or transient ischemic attack [4, 5]. However, the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation recommends replacing the CHADS₂ score with the more comprehensive CHA₂DS₂-VAsC score in order to define stroke risk in those individuals at low risk [6]. The CHA₂DS₂-VAsC score adds the following risk factors to the CHADS₂ score: Age 65–74 years, Vascular Disease, and Sex Category (Female). Two points are assigned to the following risk factors: Age ≥ 75 years and a history of prior Stroke or transient ischemic attack [6].

1.2 Oral Anticoagulants

Although warfarin, a vitamin K antagonist, has been the standard of care for stroke prevention in AF patients since it was introduced approximately 60 years ago [7], there are several limitations associated with its use, such as potential drug interactions, the need to maintain a consistent vitamin K diet, the need for frequent INR monitoring, and the clinical importance of keeping the dose within the therapeutic range [8]. However, several new oral anticoagulants have recently been approved for use. Dabigatran, rivaroxaban, and apixaban have been approved by the US Food and Drug Administration (FDA) to reduce the risk of stroke in NVAF patients. Advantages of these drugs are that they have a quick onset/offset of action [9], and do not have the vitamin K food interactions or the required International Normalized Ratio (INR) monitoring associated with warfarin. Apixaban and dabigatran 150 mg significantly reduced stroke or systemic embolism when compared to warfarin in the ARISTOTLE [10] and RE-LY [11] clinical trials, respectively, while rivaroxaban demonstrated non-inferiority when compared to warfarin in the ROCKET-AF [12] clinical trial. In addition, the risk of major bleeding was significantly reduced with apixaban, while dabigatran 150 mg and rivaroxaban did not result in significantly lower rates of major bleeding when compared to warfarin. Among the currently available oral anticoagulant medications to reduce the risk of stroke in NVAF patients, rivaroxaban and warfarin are recommended to be taken once a day and dabigatran and apixaban are recommended to be taken twice a day.

Patients with NVAF may have other co-morbid conditions that require them to take chronic medications. Also, little is known about what chronic medications patients with NVAF take, and the likelihood that NVAF patients take chronic medications other than oral anticoagulants more than once per day, in the context of an NVAF population profile in a real world setting.

1.3 Study Objective

The objective of this study was to describe the demographic and clinical characteristics of patients with NVAF with at least one risk factor for stroke, and estimate the proportion of these patients that take chronic medications more than once per day.

2 Methods

2.1 Data Source

De-identified data for this study were obtained from the MarketScan[®] Commercial Claims and Encounters

(MarketScan) database, constructed and maintained by Truven Health. The MarketScan database consists of reimbursed health care claims for employees, retirees, and their dependents of over 250 medium and large employers and health plans throughout the USA. These employers self-insure their enrollees through employer sponsored health plans. The MarketScan database includes claims information from more than 130 payers, and describes the healthcare service use and expenditures for approximately 97 million individuals per year. The database is divided into subsections, including inpatient claims, outpatient claims, outpatient prescription drug claims, and enrollment information. Claims data in each of the subsections contain a unique patient identifier (de-identified) and include information on patient age, gender, geographic location, and type of health plan. The study used de-identified data from 1 January 2008 through 30 September 2012.

2.2 Study Sample

Patients 18 years of age and older with at least two outpatient claims with a diagnosis of AF at least 30 days apart were identified using the International Classification of Disease, 9th Edition (ICD-9) code 427.31. Patients with any evidence of rheumatic mitral stenosis or a prosthetic heart valve (ICD-9 codes 394.4, 394.2, 396.0, 396.1, 396.8, 746.5, V42.2, or V43.3; or Current Procedural Terminology codes 33405, 33420, 33422, 33425, 33426, 33427, 33430, or 33496) were excluded. Finally, only patients with a CHADS₂ score of at least 1 were included in the study sample.

Patients were identified in the MarketScan database as illustrated in Fig. 1. The identification period started on 1 July 2008 to ensure a 6 month baseline period and ended on 30 September 2011 to ensure at least 12 months of follow-up. The date of the first qualifying NVAF visit was defined as the study index date. The presence of co-morbid conditions was assessed during the 6 month baseline period, and use of chronic medications was tracked during the 12 month follow-up period. Patients were required to be

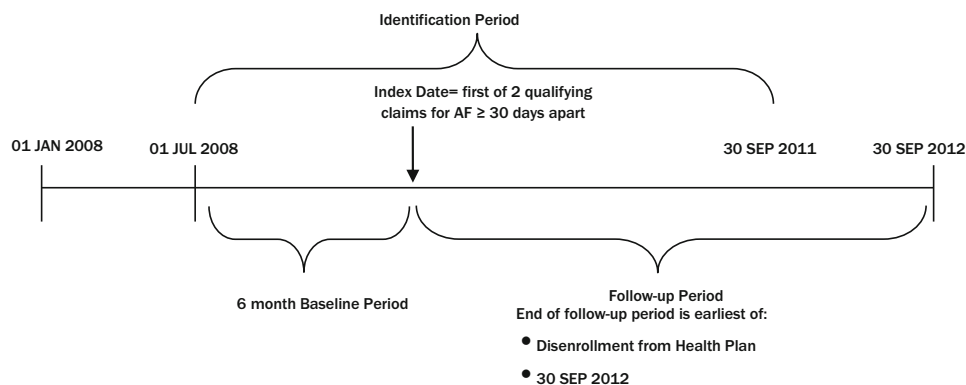
continuously enrolled during the 18 month study period (Fig. 1).

2.3 Study Design

For each medication prescribed to each patient (excluding oral anticoagulants), the total number of days supplied was determined by summing the days supply for each prescription for the medication during the follow-up period. Chronic medications were defined as those with at least 90 total days supply. The majority of non-oral prescription medications (e.g., topicals, creams, ointments, patches) were not included in this list of chronic medications. Oral medications that were also not included were analgesics, anti-infectives, laxatives, and other medications that could be used acutely or on an as needed basis, or for which the frequency of the maintenance medication may be different when prescribed for an acute indication. We also did not include over-the-counter drugs, such as aspirin, since use of these drugs cannot be reliably captured in claims data.

For each chronic medication identified, the FDA approved prescribing information was examined to determine the recommended frequency of administration. Chronic medications were classified as once daily versus more than once daily according to the prescribing information. In addition, chronic medications were also classified as being taken in the morning if the prescribing information indicated that the medication should be taken in the morning or on an empty stomach, or classified as being taken in the evening if the prescribing information indicated that the medication should be taken in the evening, with the largest meal, or at bedtime. In cases where the prescribing information did not explicitly indicate when the medication should be taken, or if the frequency of administration depended on clinical factors or symptoms, the number of prescribed “dosage units” (e.g., tablets or capsules) per day was computed by dividing the number of dosage units prescribed by the days supply. For these medications, the total number of milligrams of medication taken each day

Fig. 1 Identification period for the non-valvular atrial fibrillation (NVAF) study population



was also determined by multiplying the medication strength by the number of dosage units per day.

2.4 Medication Portfolio

A “medication portfolio” was developed for each NVAF patient to characterize the frequency with which the patient took chronic medications, other than oral anticoagulants, on a daily basis. Patients were identified as taking chronic medications more than once per day if any of the following were true: (i) the medication portfolio included a drug that should be taken more than once per day per the drug’s prescribing information; (ii) the medication portfolio included a drug that should be taken in the morning and another drug that should be taken in the evening; or (iii) the medication portfolio included a drug for which the frequency of administration was unclear, the number of dosage units per day was greater than 1, and the total milligrams per day was equal to an available dose of the medication. In this last scenario, if the patient was prescribed multiple dosage units per day for a daily dose of medication that could have been supplied in a single dosage unit, then we assume that patient was taking the medication more than once per day. Consider the following example. Suppose a patient was prescribed a 30 day supply of 60 bupropion SR 100 mg tablets, which can be dosed differently depending on whether the patient has hepatic impairment. For this hypothetical prescription, there are two tablets to be taken each day for a total daily dose of 200 mg. Since there is a 200 mg tablet strength also available for this medication, we assume that the patient was instructed to take each of the 100 mg tablets at different times of the day, since they would likely have been prescribed the 200 mg tablet if the physician intended that the patient take the entire 200 mg daily dose at once.

2.5 Analysis

Demographic and clinical measures were constructed to describe the characteristics of the study sample such as age, gender, geographic region, and CHADS₂ and CHA₂DS₂-VASc risk categories. The proportion of NVAF patients with CHADS₂ ≥ 1 that took chronic medications, other than anticoagulants, more than once per day was then determined. Patients who took medications more than once per day were stratified by either not taking an anticoagulant or by taking warfarin, dabigatran, or rivaroxaban. Apixaban was not included as an option because it was not approved for use until December 2012 and our data were collected only through September 2012; aspirin was not included because it is available over the counter and is not reliably captured in claims data. When a patient has been prescribed more than one anticoagulant during the follow-up

period, they were assigned to the group according to the anticoagulant that was prescribed for the longest duration of the 90 day follow-up period. As a sensitivity analysis, we also classified patients according to their oral anticoagulation therapy on the last day of the follow-up period. Consistent with the published literature (e.g., Amin et al. [16]), patients having more than a 60 day gap in refilling warfarin were categorized as being “off warfarin.”

3 Results

Overall, 324,172 NVAF patients were selected for the study. Characteristics of the sample are presented in Table 1. The average age of the study sample was 75.3 and the mean CHADS₂ and CHA₂DS₂-VASc scores were

Table 1 Characteristics of the non-valvular atrial fibrillation (NVAF) sample ($N = 324,172$)

Characteristic	<i>N</i>	%
Age (years)		
Mean ± SD	75.3 ± 11.8	
Median	78	
CHADS ₂		
Mean ± SD	1.51 ± 0.66	
Median	1	
CHA ₂ DS ₂ -VASc		
Mean ± SD	3.08 ± 1.23	
Median	3	
Male gender	177,126	54.6
Geographic region (USA)		
North East	53,980	16.7
North Central	108,349	33.4
South	106,798	32.9
West	54,454	16.8
Unknown	591	0.2
CHADS ₂ /CHA ₂ DS ₂ -VASc risk factors		
Congestive heart failure	56,026	17.3
Hypertension	169,550	52.3
Age ≥ 75 years	196,735	60.7
Diabetes	47,631	14.7
Prior stroke/TIA	8969	2.8
Vascular disease	94,115	29.0
Age 65–74 years	49,578	15.3
Sex category (female)	147,046	45.4

SD standard deviation, *CHADS₂* Congestive Heart Failure, Hypertension, Age ≥ 75 years, Diabetes Mellitus, and Prior Stroke or Transient Ischemic Attack, *CHA₂DS₂-VASc* Congestive Heart Failure, Hypertension, Age ≥ 75 years, Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack, Vascular Disease, Age 65–74 years, and Sex Category (Female Gender). Derived from NVAF patients with CHADS₂ ≥ 1

Table 2 Non-valvular atrial fibrillation (NVAF) patients prescribed chronic medications more than once per day in the last 90 days

Medication Group	Number of Patients	% of Patients	Patients Prescribed Chronic Medications	% Patients Prescribed Chronic Medications	Patients Prescribed Chronic Medications >1 per Day	% of All Patients	% of Chronic Medication Patients
All patients	324,172		299,716	92.5	215,527	66.5	71.9
No anticoagulant	151,761	46.8	130,302	85.9	91,580	60.3	70.3
Any anticoagulant	172,411	53.2	169,414	98.3	123,947	71.9	73.2
Warfarin	162,871	50.2	159,997	98.2	116,732	71.7	73.0
Dabigatran	9358	2.9	9237	98.7	7082	75.7	76.7
Rivaroxaban	182	0.1	180	98.9	133	73.1	73.9

1.51 ± 0.66 and 3.08 ± 1.23, respectively. Over half (54.6 %) of the patients were male. The study sample was mostly from the North Central (33.4 %) and Southern (32.9 %) geographic areas of the USA. The most common CHADS₂/CHA₂DS₂-VASc risk factor was age 75 years or older (60.7 %), followed by having a diagnosis of hypertension (52.3 %). There was substantial overlap among these risk factors, as evidenced by the fact that the percentages across CHADS₂ / CHA₂DS₂-VASc risk categories sum to well over 100 %.

Of the total number of NVAF patients identified, 299,716 (92.5 %) were prescribed chronic medications other than oral anticoagulants, and 215,527 (66.5 %; 95 % confidence interval [CI] 66.4–66.6) were identified as taking these medications more than once per day (Table 2). Among patients who were prescribed chronic medications, 71.9 % (95 % CI: 71.8–72.0) were identified as taking their medications more than once per day.

The percentages of NVAF patients prescribed chronic medications other than oral anticoagulants more than once per day by anticoagulation therapy group are also presented in Table 2. Nearly half of all patients (46.8 %) were not on prescription oral anticoagulation therapy in the last 90 days of the follow-up period. Of the remaining population (53.2 %), warfarin was the most common therapy (50.2 % of the sample), followed by dabigatran (2.9 %) and rivaroxaban (0.1 %).

The percentage of patients who were taking chronic medications more than once per day was smaller in the no anticoagulant group than among patients on an anticoagulant (60.3 vs. 71.9 %, respectively). Among those patients receiving anticoagulants, the percentage was highest for patients on dabigatran (75.7 %) with small differences across the individual anticoagulant groups. Results appear similar when defining the anticoagulation treatment groups according to the medication they were taking on the last day of the follow-up period.

Among the 299,716 NVAF patients who took chronic medications, the mean number of medications taken was 6.9 and the median was 6. The mean number of therapeutic

Table 3 Top 25 most commonly prescribed therapeutic classes of medications in the 12 months following the first diagnosis of non-valvular atrial fibrillation (NVAF)

Therapeutic class	N	%
Beta blockers ^a	194,461	60.0
Antihyperlipidemic drugs, NEC	173,680	53.6
Calcium channel blockers	108,558	33.5
ACE inhibitors	104,082	32.1
Loop diuretics	100,383	31.0
Gastrointestinal drugs, NEC	76,905	23.7
Cardiac drugs, NEC	70,193	21.7
Cardiac glycosides	66,534	20.5
Thyroid/hormones	63,348	19.5
Potassium supplements	62,999	19.4
Antidepressants	60,060	18.5
Miscellaneous therapeutic agents, NEC ^b	56,629	17.5
Antiarrhythmic agents	56,103	17.3
Antidiabetic agents, miscellaneous	47,539	14.7
Antiplatelet agents, NEC	33,027	10.2
Thiazides and related diuretics	32,452	10.0
Sulfonylurea antidiabetic agents	31,281	9.6
Potassium-sparing diuretics	30,582	9.4
Adrenals and combinations, NEC	30,530	9.4
Benzodiazepines	26,853	8.3
Hypotensive agents, NEC	25,540	7.9
Opiate agonists	22,947	7.1
Vasodilating agents, NEC	22,626	7.0
Insulin agents	22,139	6.8
Antigout agents, NEC	22,125	6.8

NEC not elsewhere classified

^a Cardiac class of medications only

^b Medications in this class included, but were not limited to, finasteride, tamsulosin, dutasteride, alfuzosin, and the bisphosphonate class of medications

classes was 6.4 and the median was 6. The most commonly prescribed therapeutic classes of medications are listed in Table 3. Beta blockers and antihyperlipidemic drugs were

Table 4 Top therapeutic classes of medications and co-morbidities by CHADS₂ score and age in the 12 months following the first diagnosis of non-valvular atrial fibrillation (NVAF)

CHADS ₂	Age			
	2+	<65	65–74	75+
Therapeutic class				
Beta blockers	58.4 %	61.7 %	61.1 %	64.2 %
Antihyperlipidemic	52.0 %	55.3 %	51.2 %	63.0 %
Calcium channel	32.2 %	38.8 %	35.7 %	36.8 %
ACE inhibitors	30.7 %	35.0 %	31.8 %	36.5 %
Loop diuretics	25.2 %	33.8 %	23.0 %	30.6 %
Gastrointestinal	21.9 %	26.1 %	21.4 %	26.2 %
Cardiac glycosides	20.2 %	23.8 %	21.1 %	25.6 %
Cardiac drugs, NEC	20.0 %	23.7 %	20.9 %	23.2 %
Thyroid/hormones	18.2 %	21.2 %	20.4 %	20.9 %
Antiarrhythmic	17.5 %	20.8 %	19.1 %	19.9 %
Comorbidities				
Chronic pulmonary disease	10.8 %	34.9 %	16.5 %	20.4 %
Diabetes	10.7 %	20.2 %	10.5 %	19.1 %
Cancer	8.3 %	18.6 %	10.0 %	17.0 %
Peripheral vascular disease	5.9 %	12.0 %	5.2 %	10.6 %
Congestive heart failure	4.6 %	10.9 %	5.0 %	9.3 %
Renal disease	3.4 %	9.3 %	4.7 %	7.7 %
Cerebrovascular disease	3.1 %	5.1 %	4.2 %	7.0 %
Myocardial infarction	2.2 %	4.0 %	3.7 %	4.2 %
				24.1 %
				22.8 %
				22.2 %
				21.1 %
				21.1 %
				16.8 %
				15.2 %
				14.5 %
				10.5 %
				9.6 %
				5.7 %
				3.4 %
				3.1 %

the most common therapeutic classes and were taken by 60.0 and 53.6 % of those in our study sample, respectively.

Table 4 illustrates the most common therapeutic classes of medications and co-morbidities by CHADS₂ score and age. Beta blockers were the most common class of medication across both CHADS₂ score categories and all age groups (58.4 % for CHADS₂ = 1 and 61.7 % for CHADS₂ ≥ 2; and 61.1, 64.2, and 58.3 % for ages <65, 65–74, and 75+, respectively). The next most commonly prescribed chronic medications were antihyperlipidemics, calcium channel blockers, ACE Inhibitors, and loop diuretics, which generally increased with CHADS₂ score and peaked in the 65- to 74-year age group.

Congestive heart failure was the most common co-morbidity for the CHADS₂ ≥ 2 score category (34.9 %) and all age groups (16.5, 20.4, and 16.8 % for ages <65, 65–74, and 75+ years, respectively), while chronic pulmonary disease was the most common co-morbidity for the CHADS₂ = 1 score category (10.8 %). Diabetes and chronic pulmonary disease were the next most common co-morbidities for the CHADS₂ ≥ 2 score category and all age groups, while diabetes and cancer were the next most common co-morbidities for the CHADS₂ = 1 score category. Table 4 highlights that NVAF patients are prescribed multiple medications from several therapeutic classes, have various co-morbidities, and, therefore, underscores the clinical complexity of the NVAF patient.

4 Discussion

This study examined the clinical and demographic characteristics of patients with NVAF who have at least one CHADS₂ risk factor for stroke in a real world setting. We found that 92.5 % of these patients take chronic medications other than oral anticoagulants, and of these patients, 71.9 % take these chronic medications more than once per day. We also found that among our sample of NVAF patients with a CHADS₂ score greater than one, the average CHADS₂ and CHA₂DS₂-VASc scores were 1.51 and 3.08, respectively, with patients taking an average of 6.9 chronic medications from an average of 6.4 therapeutic classes. These results underscore the clinical complexity of NVAF patients.

Many factors go into choice of drug therapy. Once daily administration, versus medications that must be taken multiple times per day, may be an important factor affecting drug choice. The relationship between frequency of administration and adherence has been examined in previous studies. Results have been mixed, with some studies showing that once a day drugs are more convenient for patients, which may result in better adherence [13, 14], while a review by Claxton et al. found that there was no

significant difference in compliance between once daily versus twice daily regimens [15].

Although previous studies have described characteristics of patients with NVAF and patterns of oral anticoagulant use in this patient population [17, 18], this retrospective database study examines the extent to which patients with NVAF take a variety of different chronic medications other than oral anticoagulants more than once a day. Compared to the earlier Phase III clinical trials with novel oral anticoagulants [19], our study sample had approximately the same age distribution [10–12], although the proportion of the sample that was male was higher in all the Phase III clinical studies compared to our study sample. The average CHADS₂ score for our sample was slightly lower than that seen in the Phase III trials [1.51 vs. 2.1 for both the RE-LY (dabigatran) and ARISTOTLE (apixaban) Phase III studies, and 3.5 for the ROCKET-AF (rivaroxaban) Phase III study], although this is most likely due to differences in the study design and methods across these studies.

The patient demographic and stroke risk characteristics of our study sample are also comparable to earlier MarketScan studies, as well as the ORBIT-AF Registry from 174 community based outpatient practices enrolled from 2010–2011 [20]. Studies by Zimetbaum et al. [17], Casciano et al. [5], and Naccarelli et al. [18] that used MarketScan data from 2003–2007, 2003–2007, and 2004–2005, respectively, found similar distributions of age and gender for their NVAF samples. As for stroke risk factors contributing to the CHADS₂ score, hypertension accounted for the largest percentage in all of the previously noted studies (Phase III clinical trial and MarketScan studies). CHF was the second most common stroke risk factor in all studies, except for the Casciano et al. [5] study, where diabetes was the second most common and CHF was the third most common.

In our study, there were 97,535,597 active patients in the MarketScan database (2013), with 1,499,871 (1.54 %) of those patients with at least one diagnosis of atrial fibrillation. When comparing our study sample to an earlier MarketScan study by Naccarelli [18], there were 21,648,681 active patients in their MarketScan database (2004–2005), with 313,382 (1.45 %) of those patients only having a diagnosis of atrial fibrillation. When comparing our study to the US Census population in 2010 of an estimated 308.7 million citizens [22], the annual prevalence of atrial fibrillation in 2010 was estimated at 5.2 million (1.68 %) cases in the US general population [23]. Colilla states that the prevalence of atrial fibrillation is projected to be 12.1 million by 2030 and is the result of an aging population and that the incidence rate of atrial fibrillation is also increasing [23].

It is interesting that almost half (46.8 %) of our sample of NVAF patients with CHADS₂ ≥ 1 received no oral

anticoagulant treatment. This is comparable to the rate found by Zimetbaum et al. (42.6 %) in their study of MarketScan data from 2003 through 2007 [17]. Some of these patients may be taking aspirin over the counter, which would not be captured in our claims database. In addition, 64,826 of the 135,964 (47.7 %) patients in our sample with CHADS₂ ≥ 2 and 135,956 of the 295,311 (46.0 %) patients with CHA₂DS₂-VASc ≥ 2 received no oral anticoagulation treatment, which according to the recent 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation, suggests suboptimal use of NVAf thromboprophylaxis [6, 21]. Among those receiving oral anticoagulant treatment, warfarin remains the dominant treatment modality (50.2 %), despite the need for maintaining a consistent diet with respect to vitamin K intake and frequent INR monitoring. Very few patients received dabigatran (2.9 %) or rivaroxaban (0.1 %), most likely due to their recent introduction to the market.

4.1 Limitations

Although this study has several strengths, such as the large sample size, the ability to track outpatient prescriptions and refills over time, and the nationwide sample, several limitations deserve comment. Primary among these is the fact that we cannot determine what instructions patients are given with respect to frequency of administration; we can only infer the frequency with which patients take chronic medications based on the FDA approved prescribing information and other characteristics of the medications and/or prescription records. For example, we categorize a patient that has been prescribed two dosage units a day as a patient that takes medication twice daily (barring any additional information) if the sum of the milligrams is equal to an available dose of the same medication. While this is the best categorization for the majority of patients that fall under this scenario, we recognize that patients may be incorrectly categorized if in fact they are instructed to take “up to” two dosage units a day to allow them flexibility in treating their condition (for example, someone who is instructed to take different doses based on blood pressure readings). In this last scenario, we recognize that the patient with flexible dosing instructions is “at risk” of needing to take their medication more than once per day and categorize them accordingly. We also acknowledge that some patients may be prescribed two smaller dosage units to be taken simultaneously, instead of a larger dosage unit strength, to allow for dosing titration, flexibility and ease of administration.

Another limitation is that our ability to identify comorbid conditions for computing the CHADS₂ and CHA₂DS₂-VASc measures was limited by the 6 month

baseline period used to identify these conditions. In addition, because we rely on claims data and not detailed clinical data, we may underestimate the percentage of patients with some components of the CHADS₂ measure, such as history of CHF, hypertension, diabetes, and prior stroke/TIA, which could result in a lower calculated CHADS₂ score.

Also, another limitation is that the CHA₂DS₂-VASc calculations were based on the selection criteria in the study, a CHADS₂ score of ≥ 1 , which would have underestimated capturing those patients with criteria specific to the CHA₂DS₂-VASc scoring system such as vascular disease, age 65–74 years and female gender. Finally, use of over-the-counter medications such as aspirin is likely to be under-reported in the claims data; therefore, use of aspirin was not assessed in this study.

5 Conclusion

Our study demonstrates that patients with NVAf are clinically complex, and often take chronic medications, other than oral anticoagulants, more than once a day and that this may diminish the potential convenience of a once daily oral anticoagulant medication regimen. Further, the clinical complexity of this patient population may require consideration of other factors when deciding between a once a day versus a more than once a day dosing of an oral anticoagulant. More research is needed to understand the impact of prescribing a once daily oral anticoagulant medication versus a more than once a day oral anticoagulant medication on adherence when patients are already taking chronic medications more than once per day.

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Compliance with Ethical Standards

Ethical approval This article does not contain any studies with human participants performed by any of the authors. This study was approved by the Institutional Review Board at the Penn State Health, Milton S. Hershey Medical Center, Hershey, PA, USA.

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