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Underuse of Oral Anticoagulants in Privately Insured Patients with Atrial Fibrillation: A Population Being Targeted by the IMplementation of a Randomized Controlled Trial to ImProve Treatment with Oral AntiCoagulanTs in Patients with Atrial Fibrillation (IMPACT-AFib trial)

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Abstract

Background: Although oral anticoagulants (OACs) have been shown to substantially reduce the risk of stroke and other thromboembolic events in patients with atrial fibrillation (AF), these medications are significantly underutilized in clinical practice. However, many studies showing underuse of OACs predated the advent of the non-vitamin K antagonist oral anticoagulants. We conducted this study to examine use of OACs in a large commercially insured population, which was enrolled in a randomized trial to address underuse of OACs.

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Methods: Administrative health care claims data from 5 research partners who participate in the FDA-Catalyst, a program of the Sentinel Initiative, were queried in September 2017 to identify patients ≥30 years old with ≥365 days of medical/pharmacy coverage, ≥2 diagnosis codes for AF, a CHA_2DS_2-VASc score ≥2, absence of selected conditions for which OAC use is contraindicated, and no evidence of OAC use in the 365 days prior to the index AF diagnosis. The identified cohort has been targeted for enrollment in the IMPACT-AFib trial, a randomized clinical trial evaluating the effect of patient and provider education interventions on the use of OACs.

Results: A total of 241,044 AF patients met the cohort eligibility criteria prior to assessment of OAC treatment. In this cohort, 220,869 (92%) patients were ≥ 65 years old and 94,459 (39%) patients were ≥ 80 years old. Patients were randomized to early or delayed intervention. Among 120,522 patients randomized to the early intervention arm, 43,826 (36%) had no evidence of OAC use in the prior 12 months. Compared with patients with evidence of an OAC use in the prior 12 months, patients without OAC use were more likely to be 80 years of age or older, women, and residents of the Midwest region. Patients without OAC use were more likely to have a history of anemia (52% vs. 48%) and less likely to have diabetes (39% vs. 44%), a history of stroke or TIA (17% vs. 20%), and a history of heart failure (40% vs. 48%). The mean CHA_2DS_2-VASc score was 5 for both the OAC and no-OAC recipients; however, patients with no OAC use had a higher ATRIA score (39% vs. 35%).

Conclusions: Data from a large privately insured population show that despite a high risk of stroke, over one third of patients with AF and no obvious contraindications to an OAC were not treated with an OAC in the prior 12 months. Thus, there is an unmet medical need for studies that develop evidence-based interventions that could lead to greater use of OACs in patients with AF who are at risk for stroke.

Atrial fibrillation (AF) affects more than 5 million Americans, and this number is increasing as the United States population ages.[1–4] AF can result in substantial mortality and morbidity including thromboembolic events, myocardial infarction, and heart failure.[1–7] Of the thromboembolic events that occur as a result of AF, stroke is by far the most common and serious. When stroke occurs as a complication of AF, it is more disabling and deadly than other strokes.[1] Therefore, it is imperative to identify all patients with AF who are at risk of stroke, especially because this risk can be substantially reduced with oral anticoagulation. Identifying AF patients at risk for stroke can be accomplished by using well-established risk scores. One such risk score is the CHA_2DS_2-VASc score (C=congestive heart failure, H=hypertension, A=age, D=diabetes, S=prior stroke or transient ischemic attack (TIA), V=vascular disease, S=sex).[2] The American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines recommend using the CHA_2DS_2-VASc score in clinical practice and, in the absence of absolute contraindications, initiating an oral anticoagulant (OAC) promptly for a score of ≥ 2.[2]

Although oral anticoagulation is very effective for stroke prevention in AF, studies have shown that about half of AF patients with a $CHA2DS_2$-VASc score of ≥ 2 are not on an OAC.[8–11] However, most of these studies predated the non-vitamin K antagonist oral anticoagulants (NOACs).[12–15] Our goal in this paper is therefore to examine current utilization of OACs for AF among privately insured individuals, including both commercially insured and Medicare Advantage populations. To that end, we used electronic

health data from 5 large research partners, using a common data model and distributed querying methods developed under the FDA Sentinel Initiative. FDA-Catalyst is the Sentinel component that leverages the ability of Sentinel network partners to engage in interventions or interactions with health plan members and providers,[16] and it provides the infrastructure for the IMplementation of a randomized controlled trial to imProve treatment with oral AntiCoagulanTs in patients with Atrial Fibrillation (IMPACT-AFib trial) that was launched in 2017. The main purpose of the IMPACT-AFib trial is to assess the effect of patient and provider education interventions on the use of OACs among patients with AF and with guideline-based indications for oral anticoagulation (CHA_2DS_2-VASc score of 2 or greater).[17]

Methods

Data sources

The data source for this FDA-Catalyst study was the Sentinel distributed network made up of electronic health data locally transformed to a Common Data Model. Each of the five participating research partners maintains a local version of its own data in a Common Data Model format in order to enable distributed queries.[18] To ensure privacy and data protection, queries are distributed and results are returned through a secure portal. Health plan members older than 65 years of age include both commercially insured and Medicare Advantage beneficiaries.

Study Population

Administrative health care claims data from 5 research partners were queried in September 2017 to identify patients ≥30 years old with ≥365 days of medical/pharmacy coverage, ≥2 diagnosis codes for AF (1 within 365 days of research partners' data availability end date), a CHA_2DS_2-VASc score ≥2, absence of specific conditions for which OAC use is contraindicated, and no OAC treatment in the 365 days prior to the research partners' data abstraction end date. Contraindications to OAC use were intracranial hemorrhage, pregnancy, or hospitalization for bleeding within the prior 6 months. Patients were also excluded if they had a condition other than AF that requires anticoagulation such as deep vein thrombosis, pulmonary embolism, or a mechanical cardiac valve. Patients with dispensing of a P2Y12 antagonist (e.g. clopidogrel and prasugrel) within the 90 days prior to cohort identification were also excluded. Treatment was defined as at least 1 bill for dispensing of an OAC or ≥4 INR test results or procedure codes, to capture use of warfarin without a claim being made. Research partners' end dates for data query ranged from June 2016 through November 2016.

The study protocol specified the method of identifying all patients eligible for treatment with an OAC and for randomizing them to early or delayed intervention. OAC exposure status was determined in the early intervention group. It will be determined in the delayed intervention group after 12 months, when the delayed intervention to the provider only will occur. Evidence of OAC use was defined as at least one dispensing of an OAC (warfarin, coumadin, dabigatran, rivaroxaban, apixaban or edoxaban) in the prior 365 days or at least four International Normalized Ratio (INR) test results based on procedure codes in the prior

365 days. INR testing is performed regularly in users of warfarin to determine whether the medication effect is in the therapeutic range, thus frequent INRs are another method to identify who is likely being treated with warfarin. Also, INRs were included because users of warfarin may not have dispensings recorded in their claims data due to low cost options that are paid out of pocket. Because individuals eligible for OAC treatment were randomized to the early and delayed intervention groups, analysis of the treatment status and other characteristics of the early intervention group are expected to be representative of the entire population of these health plans.

Statistical Analysis

Patients with evidence of OAC use in the prior 12 months were characterized and compared with patients with no OAC use in the prior 12 months. Categorical variables are presented as counts (percentages), and continuous variables as means (standard deviations [SD]). Categorical variables were compared using the Pearson's chi-square or Fisher's exact test, as appropriate. Continuous variables were compared using two-sample t-test. P-values <0.05 from two-sided tests were considered statistically significant. Adjustments were not made for multiple comparisons. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 309,859 patients were identified as having 2 or more diagnoses of AF with at least 1 diagnosis within the12 months prior to the last date used for cohort identification. Prior to assessing OAC use at baseline defined as any OAC use in the prior 12 months, 241,044 patients met guideline criteria for OAC therapy. Reasons for excluding patients (i.e. reasons for the drop from 309,859 to 241,044 patients) are shown in Figure 1 (some patients may have had more than 1 exclusion criterion). Table 1 shows the baseline characteristics of the 241,044 patients who met guideline criteria for OAC therapy. In the overall cohort of eligible AF patients, 220,869 (92%) were ≥ 65 years old with 94,459 (39%) patients ≥ 80 years old. Almost half of the cohort (112,500, 47%) were women. The most common comorbidities included hypertension (229,059, 95%), anemia (118,343, 49%), heart failure (108,588, 45%), diabetes (100,438, 42%), and a history of cerebrovascular or thromboembolic event (75,434, 31%). Prior stroke or TIA was present in 45,262 (19%) patients. There were 106,084 (44%) patients with CHA_2DS_2VASc scores of 4 and 5; the overall mean score was 5. Only 12% had a CHA_2DS_2VASc score of 2. A total of 120,642 (51%) patients had an intermediate or high Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) score for bleeding (score is based on prior stroke, age, sex, history of heart failure, hypertension, diabetes, proteinuria and renal function). The majority of patients (206,381, 86%) had not been hospitalized in the 6 months preceding cohort identification. As shown in Table 1, the baseline characteristics were well balanced between the early and delayed intervention groups.

Table 2 shows the baseline characteristics of the 120,552 patients randomized to the early intervention group. Among these, 43,826 (36%) did not have evidence of OAC use in the prior 12 months. Compared with patients with OAC use in the prior 12 months, patients

without OAC use were more likely to be 80 years of age or older, women, and residents of the Midwest. Patients without evidence of an OAC in the prior 12 months were more likely to have a history of anemia and less likely to have diabetes, a history of stroke or TIA, and a history of heart failure. The mean CHA_2DS_2-VASc score for both groups was 5; however, more patients with no OAC use in the prior 12 months had a high ATRIA score.

Discussion

This study has three main findings. First, despite the morbidity burden with a high CHA_2DS_2-VASc score and the fact that patients with a recent significant bleeding event were excluded from this analysis, the number of patients with AF and with no evidence of OAC use in the prior 12 months was high (36%). Second, in univariable analyses, clinical and geographic differences exist between AF patients treated with an OAC use in the prior 12 months and those not treated. Third, patients identified for potential enrollment in the IMPACT-AFib trial were relatively old and had a high burden of morbidity.

Although patients we identified were at a high risk of stroke and the cohort was derived after excluding patients with a prior intracranial hemorrhage and patients with a hospitalization for bleeding in the past 6 months, a significant number of patients (43,826; 36%) were not using an OAC in the prior 12 months. Underuse of OACs in AF patients has been reported previously with rates exceeding 50% in some studies.[8–10] Reasons for underutilization of vitamin K antagonists (an OAC) in patients with AF were examined in the AVERROES (Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trial. Although non-compliance was among the main reasons for not using a vitamin K antagonist, the majority of patients were deemed not to be candidates for a VKA based on multiple reasons.[19]

Prior to this analysis, in the United States, factors associated with underuse of OACs in clinical practice had not been examined among the large population of individuals with commercial or Medicare Advantage coverage. Although several studies have investigated patterns of use of OACs, these studies did not report on reasons for underuse of OACs.[8–10] One study in the United States investigated reasons for warfarin discontinuation in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) database and found the most common reasons were physician preference, patient refusal, and bleeding events.[20] Most studies that have examined factors associated with underutilization of OACs in clinical practice were conducted outside the United States. One retrospective cross-sectional study was conducted in Sweden and aimed to identify reasons for underutilization of OACs in patients with AF. Among 2,274 patients with AF, 1187 (52%) were not treated with an OAC. Of the untreated patients, 19% either had a CHA_2DS_2-VASc score < 2 or had declined or had experienced an adverse event other than bleeding on warfarin therapy. The most common reason (38% of patients) for not using an OAC was presence of risk factors for bleeding.[21] One study used the Global Anticoagulant Registry in the FIELD (GARFIELD), a database of patients with newly diagnosed non-valvular AF. Patients were enrolled between December 2009 and October 2011 at 540 sites in 19 countries in Europe, Asia-Pacific, Central/South America, and Canada. Sites participating in

this registry were representative of the distribution of AF care settings in each country. The analysis included 10,614 adults (≥18 years) diagnosed with AF within the previous 6 weeks, with ≥1 investigator-defined stroke risk factor. Overall, 38% of patients with a $CHADS_2$ score ≥2 did not receive an OAC. This underuse resulted from physician refusal on the basis of bleeding risk, fall risk, and concern over patient non-compliance in 48% of patients. Other reasons were not clearly defined.[22]

The current study adds to the body of information on factors associated with underuse of OACs. Patients with no OAC use in the prior 12 months in this study differed significantly from patients with an OAC use in that they were more likely to be 80 years of age or older, women, and residents of the Midwest region of the United States and to have a history of anemia and a high Atria score. Underutilization of OACs in older patients and women has been reported previously; this study shows these trends in practice have persisted and calls for individualized approaches to addressing these disparities.[8,9,23] To that end, it will be important to obtain information from a diverse group of patients by age, sex, and race about what drives their decisions regarding use of an OAC and strategies that may work or not work in specific subgroups of patients.

The large size of the source population for IMPACT-Afib trial will ensure generalizability of this trial's findings to patients in the general community. Indeed, the vast majority of the patients we identified (92%) were at least 65 years old, and 39% were at least 80 years old. The morbidity burden in these patients was relatively high with 31% having had a prior history of cerebrovascular or thromboembolic event and 19% having had a prior stroke or TIA. The prevalence of hypertension was very high, and an appreciable number of patients had heart failure and diabetes. Therefore, it is not surprising that the mean CHA_2DS_2-VASc score was 5, a score that portends a high risk of stroke ranging from an annual risk of 7% to 15%.[24]

This study has some limitations. Data quality is dependent on the accuracy and completeness of documentation and coding in administrative claims data. We did not assess the days covered with an OAC or whether users in the last year had ongoing OAC use at baseline, and due to the lack of patient-level data, we were not able to create a multivariable model to evaluate factors independently associated with underuse of OACs.

Conclusions

Although patients in this study had a high CHA_2DS_2-VASc score, and therefore were at a high risk of stroke, the number of patients with AF and with no evidence of OAC use in the prior 12 months was high. Clinical and geographic differences exist between AF patients with and those without OAC use in the prior 12 months that may inform future initiatives aimed at improving utilization of OACs in eligible patients. These gaps in care underscore the importance of trials to address this problem like IMPACT-AFib, and it is indeed reassuring that patients enrolled in the IMPACT-AFib trial were relatively old and had a high burden of morbidity. This profile will likely ensure generalizability of the trial's findings to patients seen in clinical practice.

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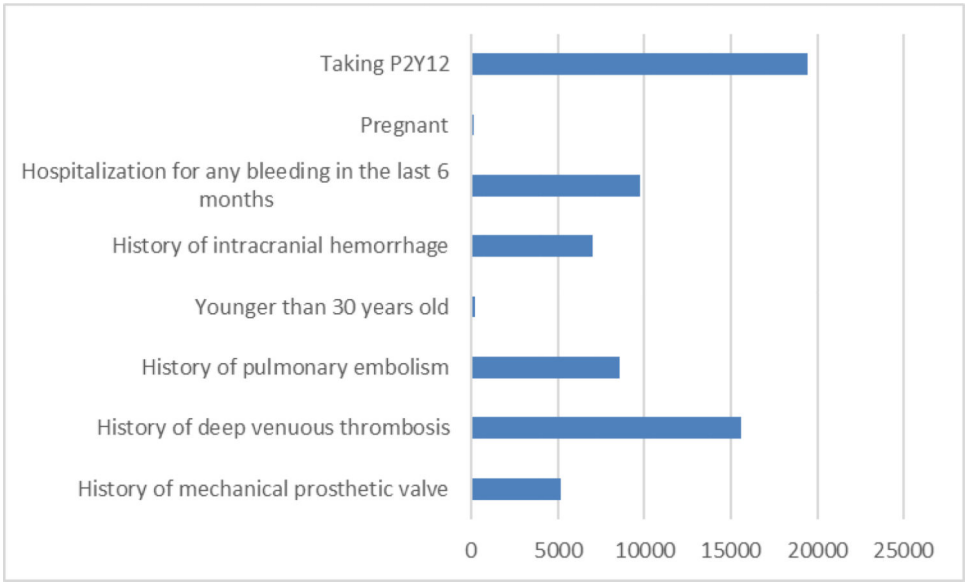

Figure 1:
Reasons for excluding patients (some patients may have had more than 1 reason)

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Table 1:

Baseline characteristics of privately insured patients with atrial fibrillation and CHA_2DS_2-VASC scores ≥2, by randomization status to early and delayed intervention cohorts

	All members meeting inclusion criteria with CHA_2DS_2-VASC scores ≥2		**Randomized to delayed intervention**		***Randomized to early intervention***		
Totals	**241,044**		**120,522**		***120,522***		
	N	**%**	**N**	**%**	***N***	***%***	***P-value***
Age							***0.69***
<30–44	646	0.3	338	0.3	*308*	*0.3*	
45–64	19,529	8.1	9,747	8.1	*9,782*	*8.1*	
65–74	74,774	31.0	37,372	31.0	*37,402*	*31.0*	
75–80+	146,095	60.6	73,065	60.6	*73,030*	*60.6*	
Female sex	112,500	47	56,085	47	56,415	47	0.18
Geographic Region							**0.09**
New England	9,778	4	4,931	4	4,847	4	
Mid-Atlantic	12,543	5	6,290	5	6,253	5	
South-Atlantic	130,707	54	65,064	54	65,643	55	
Midwest	59,317	25	29,923	25	29,394	24	
Mountain	11,702	5	5,903	5	5,799	5	
Pacific	16,941	7	8,385	7	8,556	7	
Unknown	56	0	26	0	30	0	
Anemia	118,343	49	59,076	49	59,267	49	0.44
Hypertension	229,059	95	114,470	95	114,589	95	0.26
Diabetes	100,438	42	49,941	41	50,497	42	0.02
Peripheral vascular disease	72,396	30	36,172	30	36,224	30	0.82
Prior cerebrovascular or thromboembolic event	75,434	31	37,835	31	37,599	31	0.30
Prior cerebrovascular event	54,495	23	27,206	23	27,289	23	0.69
Stroke or TIA	45,262	19	22,620	19	22,642	19	0.91

	All members meeting inclusion criteria with CHA_2DS_2-VASC scores ≥2		Randomized to delayed intervention		*Randomized to early intervention*		
Totals	**241,044**		**120,522**		***120,522***		
	N	**%**	**N**	**%**	***N***	***%***	***P-value***
TIA	34,948	15	17,495	15	17,453	15	0.81
Stroke	22,954	10	11,438	10	11,516	10	0.59
Heart failure	108,588	45	54,426	45	54,162	45	0.28
Kidney disease	16,913	7	8,392	7	8,521	7	0.30
Dialysis	7,813	3	3,917	3	3,896	3	0.81
History of MI	27,070	11	13,495	11	13,575	11	0.61
History of CABG	34,230	14	17,062	14	17,168	14	0.54
CHA_2DS_2-VASC							0.36
0–1	0	0	0	0	0	0	
2	24,413	10	12,209	10	12,204	10	
3	44,148	18	22,133	18	22,015	18	
4	56,459	23	28,154	23	28,305	24	
5	49,625	21	24,847	21	24,778	21	
6	33,941	14	17,121	14	16,820	14	
7	19,385	8	9,570	8	9,815	8	
8	10,256	4	5,105	4	5,151	4	
9	2,817	1	1,383	1	1,434	1	
Mean	*5*	*NA*	*5*	*NA*	*5*	*NA*	>0.99
SD	*1.7*	*NA*	*1.6*	*NA*	*1.7*	*NA*	
Atria score							0.44
<= 3 (low)	120,402	50	60,312	50	60,090	50	
4 (intermediate)	33,558	14	16,677	14	16,881	14	
5 (high)	87,084	36	43,533	36	43,551	36	
Hospitalizations in the prior 6 months							0.54
0	206,381	86	103,208	86	103,173	86	
1	26,934	11	13,451	11	13,483	11	

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	All members meeting inclusion criteria with CHA_2DS_2-VASC scores ≥2		Randomized to delayed intervention		*Randomized to early intervention*		
Totals	**241,044**		**120,522**		***120,522***		
	N	**%**	**N**	**%**	***N***	***%***	***P-value***
2	5,490	2	2,715	2	2,775	2	
≥3	2,239	1	1,148	1	1,091	1	

* OAC use at baseline was defined as any OAC use in the prior 12 months.

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Table 2:

Baseline characteristics by evidence of use of OACs among privately insured members with atrial fibrillation and CHA_2DS_2-VASC scores ≥2

	Patients Not Using an OAC at Baseline*		Patients Using an OAC at Baseline*		P-value
Totals	**43,826**		**76,696**		
	N	**%**	**N**	**%**	
Age					**<0.0001**
<30–44	150	0.3	158	0.2	
45–64	3,375	7.7	6,407	8.4	
65–74	13,343	30.4	24,059	31.4	
75–80+	26,958	61.5	46,072	60.1	
Female sex	21,171	48	35,244	46	**<0.0001**
Geographic Region					**<0.0001**
New England	1,245	3	3,602	5	
Mid-Atlantic	1,879	4	4,374	6	
South-Atlantic	23,488	54	42,155	55	
Midwest	12,204	28	17,190	22	
Mountain	2,074	5	3,725	5	
Pacific	2,921	7	5,635	7	
Unknown	15	0	15	0	
Anemia	22,702	52	36,565	48	**<0.0001**
Hypertension	41,247	94	73,342	96	**<0.0001**
Diabetes	17,172	39	33,325	44	**<0.0001**
Peripheral vascular disease	13,253	30	22,971	30	**0.29**

	Patients Not Using an OAC at Baseline*		Patients Using an OAC at Baseline*		P-value
Totals	**43,826**		**76,696**		
	N	**%**	**N**	**%**	
Prior cerebrovascular or thromboembolic event	14,127	32	23,472	31	**<0.0001**
Prior cerebrovascular event	9,075	21	18,214	24	**<0.0001**
Stroke or TIA	7,493	17	15,149	20	**<0.0001**
TIA	5,850	13	11,603	15	**<0.0001**
Stroke	3,547	8	7,969	10	**<0.0001**
Heart failure	17,694	40	36,468	48	**<0.0001**
Kidney disease	3,328	8	5,193	7	**<0.0001**
Dialysis	1,498	3	2,398	3	**0.006**
History of MI	5,405	12	8,170	11	**<0.0001**
History of CABG	6,529	15	10,639	14	**<0.0001**
CHA_2DS_2-VASC					**<0.0001**
0–1	0	0	0	0	
2	5,264	12	6,940	9	
3	8,240	19	13,775	18	
4	10,179	23	18,126	24	
5	8,620	20	16,158	21	
6	5,798	13	11,022	14	
7	3,374	8	6,441	8	
8	1,809	4	3,342	4	
9	542	1	892	1	
Mean	*5*	*NA*	*5*	*NA*	>0.99

	Patients Not Using an OAC at Baseline*		Patients Using an OAC at Baseline*		P-value
Totals	**43,826**		**76,696**		
	N	**%**	**N**	**%**	
SD	*1.7*	*NA*	*1.6*	*NA*	
Atria score					**<0.0001**
<= 3 (low)	20,852	48	39,238	51	
4 (intermediate)	6,021	14	10,860	14	
5 (high)	16,953	39	26,598	35	
Hospitalizations in the prior 6 months					**0.15**
0	37,382	85	65,791	86	
1	5,007	11	8,476	11	
2	1,032	2.4	1,743	2.3	
≥3	405	0.9	686	0.9	

*OAC use at baseline was defined as any OAC use in the prior 12 months.

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