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ORIGINAL RESEARCH

Anticoagulant Prescribing for Non-Valvular Atrial Fibrillation in the Veterans Health Administration

Adam J. Rose, MD, MSc; Robert Goldberg, PhD; David D. McManus, MD, ScM; Alok Kapoor, MD, MSc; Victoria Wang, BA; Weisong Liu, PhD; Hong Yu, PhD

***Background*—**Direct acting oral anticoagulants (DOACs) theoretically could contribute to addressing underuse of anticoagulation in non-valvular atrial fibrillation (NVAF). Few studies have examined this prospect, however. The potential of DOACs to address underuse of anticoagulation in NVAF could be magnified within a healthcare system that sharply limits patients' exposure to out-of-pocket copayments, such as the Veterans Health Administration (VA).

***Methods and Results*—**We used a clinical data set of all patients with NVAF treated within VA from 2007 to 2016 (n=987 373). We examined how the proportion of patients receiving any anticoagulation, and which agent was prescribed, changed over time. When first approved for VA use in 2011, DOACs constituted a tiny proportion of all prescriptions for anticoagulants (2%); by 2016, this proportion had increased to 45% of all prescriptions and 67% of new prescriptions. Patient characteristics associated with receiving a DOAC, rather than warfarin, included white race, better kidney function, fewer comorbid conditions overall, and no history of stroke or bleeding. In 2007, before the introduction of DOACs, 56% of VA patients with NVAF were receiving anticoagulation; this dipped to 44% in 2012 just after the introduction of DOACs and had risen back to 51% by 2016.

***Conclusions*—**These results do not suggest that the availability of DOACs has led to an increased proportion of patients with NVAF receiving anticoagulation, even in the context of a healthcare system that sharply limits patients' exposure to out-of-pocket copayments. **(*J Am Heart Assoc*. 2019;8:e012646. DOI: 10.1161/JAHA.119.012646.)**

Key Words: anticoagulation • atrial fibrillation • practice variation • stroke prevention • veterans

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New-onset atrial fibrillation is estimated to affect several hundred thousand American adults annually, with ≈7 million prevalent cases in the United States.[1] Atrial fibrillation is a leading cause of morbidity and mortality worldwide[2] and is a major risk factor for ischemic stroke.[3] For many years, warfarin was the only oral agent available for long-term anticoagulation for patients with various prothrombotic conditions, including atrial fibrillation. The management of many patients with atrial fibrillation has been changing in recent years, however, because of the approval of direct-acting oral anticoagulants (DOACs) for stroke prevention in patients with non-valvular atrial fibrillation (NVAF).[4] DOACs do not require the frequent laboratory testing or dose titrations that are needed to effectively manage patients with NVAF who are treated with warfarin, a therapy that is associated with considerable patient burden. The proportion of patients with NVAF who are prescribed DOACs has increased dramatically in the United States, Canada, and Europe since their introduction almost a decade ago.[4–13]

Based on data from US registries, only half of eligible patients with NVAF receive anticoagulation for stroke prevention,[14] despite the fact that the benefits of anticoagulation frequently outweigh the risks of treatment.[15,16] DOACs could increase the number of patients willing to receive oral anticoagulation for stroke prevention since many patients with NVAF decline warfarin-therapy owing to the frequency of laboratory monitoring, the possibility of drug-drug interactions, and dietary restrictions.[17] Few studies to date, however, have examined how the introduction of DOACs may have changed the overall rate of anticoagulation for patients with AF. The few studies that have been completed, however, suggest modest changes or no change, perhaps as a result of the high out-of-pocket costs associated with DOAC therapy.[5] The influence of DOACs on the rate of anticoagulation for

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Clinical Perspective

What Is New?

- In the Veterans Health Administration, in 2016, patient-level predictors of receiving a direct-acting anticoagulant for non-valvular atrial fibrillation, as opposed to warfarin, included intact renal function, lack of prior stroke, fewer comorbid conditions, and living in the Northeast region.

What Are the Clinical Implications?

- The availability of direct-acting anticoagulants has not led to an increased proportion of patients with non-valvular atrial fibrillation receiving anticoagulation, even in the context of a healthcare system that sharply limits patients' exposure to out-of-pocket copayments.
- Clinicians should choose the optimal medication for each patient based on clinical considerations, and consistent with clinical guidelines.

patients with AF, and the question of which medications are used for which patients, may be different in a system that sharply limits out of pocket costs for expensive medications, such as the Veterans Health Affairs (VA) system.[18]

The primary objective of this large observational study was to describe recent decade long trends (2007–2016) in the prescribing of DOACs and warfarin among patients with NVAF treated in a system that limits out-of-pocket medication costs to no more than $9/month. Our secondary study objective was to describe the characteristics of patients with NVAF likely to be treated with specific anticoagulant regimens during the years under study.

Methods

Data Set

We used data from the VA Corporate Data Warehouse, a source that includes patient demographics, diagnosis codes, dates of service, laboratory test results, and medications dispensed. Using diagnosis codes, we identified all patients treated in the VA system with a diagnosis of NVAF between January 1, 2007, and December 30, 2016. Patients were considered to have NVAF if they had *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) code 427.31 or *ICD-10-CM* codes I48.xx, and did not have one of the *ICD* codes listed for valvular heart disease in Table 1. We also varied the definition of what constituted valvular heart disease, ranging from not excluding any patients for this reason to a much broader definition of valvular heart disease encompassing any sort of regurgitation, stenosis, repair, or replacement of any valve, for any reason. The sample size changed somewhat because of these choices (on the order of 10%), but the results of all analyses otherwise remained virtually identical.

The study was approved by the Institutional Review Boards of the Bedford VA Medical Center, RAND Corporation, and the University of Massachusetts Medical School, with a waiver of informed consent. Because of the sensitive nature of VA data, they are only available for research by application, and in cooperation with a VA-based researcher. Inquires may be sent to virec@va.gov. Analytic code is available from the authors upon request.

Dependent Variable—Receipt of Anticoagulant Therapy

We characterized which patients with NVAF received anticoagulation within the VA system, based on having received at least 30 total days' supply of warfarin or a DOAC from a VA pharmacy. Of those who were prescribed anticoagulant therapy, we characterized which patients received a DOAC as opposed to warfarin, and among those who received a DOAC, which DOAC. Patients who received both warfarin and a DOAC were considered to have received the one they received for more days; in the event of similar usage rates, they were considered to have received the most recently dispensed drug. The DOACs were first included in the VA formulary in Fiscal Year 2011. During the years under investigation, there were 3 DOACs available from VA pharmacies, namely apixaban, dabigatran, and rivaroxaban.

Independent Variables—Patient-Level Characteristics

We characterized patients based on their age, sex, body mass index, and region of the United States (Northeast, Southeast, West, and Midwest). We characterized whether patients had a history of certain comorbid conditions (heart failure, hypertension, vascular disease, diabetes mellitus, prior bleeding, and prior stroke) using a 1-year look-back period[19] and based on the *ICD* codes in Table 1. For each patient, we computed a CHADS-VASc stroke risk score,[20,21] based on the demographics and comorbid conditions mentioned above. We calculated patient's estimated glomerular filtration rate from laboratory creatinine findings and other parameters using the Modification of Diet in Renal Disease formula.[22] This formula was selected because of its compatibility with the creatinine assays used in the VA system throughout the study period, and with the data elements available in the VA data set. For patients with multiple creatinine values during the study period, we used the most recent value. We also calculated a count of Elixhauser Comorbidities for each patient, using diagnostic codes reported as part of hospital and ambulatory encounters.[23]

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Table 1. *ICD* Codes to Define Valvular Heart Disease, Comorbid Conditions, and Stroke Risk Factors

	ICD-9-CM	*ICD-10-CM*
Valvular heart disease—diagnosis codes	394.0 Mitral stenosis 394.2 Mitral stenosis with insufficiency 396.1 Mitral stenosis with aortic insufficiency 396.8 Mitral and aortic multiple valvular disease 396.9 Mitral and aortic valve disease NOS 746.5 Congenital mitral stenosis V43.3 Heart valve replacement NEC	I05.0 Rheumatic mitral stenosis I05.2 Rheumatic mitral stenosis with insufficiency I08.0 Rheumatic disorders of both mitral and aortic valves I08.1 Rheumatic disorders of both mitral and tricuspid valves I08.3 Combined rheumatic disorders of mitral, aortic, and tricuspid valves I08.8 Other rheumatic multiple valve diseases I08.9 Rheumatic multiple valve disease, unspecified I09.81 Rheumatic heart failure I34.2 Nonrheumatic mitral valve stenosis Q23.2 Congenital mitral stenosis Q23.8 Other congenital malformations of aortic and mitral valves Q23.9 Congenital malformations of aortic and mitral valves, unspecified Z95.2 Presence of prosthetic heart valve
Valvular heart disease—procedure codes	35.02 Closed mitral valvotomy 35.12 Open mitral valvuloplasty 35.20 Replace heart valve NOS 35.22 Replace aortic valve NEC 35.24 Replace mitral valve NEC 35.26 Replace pulmonary valve NEC 35.28 Replace tricuspid valve NEC	02QG Repair of mitral valve 02RF Replacement of aortic valve 02RG Replacement of mitral valve 02RH Replacement of pulmonary valve 02RJ Replacement of tricuspid valve
Heart failure	398.91, 402.x, 404.01, 404.11, 404.03, 428.x	I42.9, I50.x
Hypertension	401.x, 402.x, 403.x, 404.x, 405.x, 437.2	I50.30, I50.40, I50.9, N03.9, N18.1, N18.2, N18.3, N18.4, N18.5, N18.6, N18.9, N19, Z99.2, I10, I11, I11.0, I11.9, I12, I12.0, I12.9, I13, I13.0, I13.1, I13.10, I13.11, I13.2, I15, I15.0, I15.1, I15.2, I15.8, I15.9, I16, I16.0, I16.1, I16.9
Vascular disease	410.x, 411.x, 412, 440.x, 441.x, 443.1, 443.89	H91.90, G40.909, E11.9, N28.9, I21.x-I24.x, I70.x
Diabetes mellitus	249.x, 250.x, 357.2, 362, 366.41	B35.1, E03.9, E23.2, E27.49, E66.9, E78.1, E78.6, G56.00, H21.1X9, H33.40, H34.9, H35.049, H40.9, H42, H43.10, H47.099, H47.20, H54.0, H54.10, H54.7, H91.90, I10, I12.0, I12.9, I70.209, K31.84, L03.039, L03.119, L89.509, L89.609, L97.209, L97.309, L97.409, L97.509, L97.519, L97.529, L97.909, L97.919, L97.929, L98.499, M54.14, M54.16, M86.9, N18.1, N18.2, N18.3, N18.4, N18.5, N18.6, N18.9, N52.1, R19.7, R80.9, Z79.4, Z99.2, E08-E13
Prior bleeding	423.0, 430, 431, 432.x, 455.2, 455.5, 455.8, 456.0, 456.2, 459.0, 530.7, 530.82, 531.01, 531.41, 531.61, 532.01, 532.21, 532.41, 532.61, 533.21, 533.4, 534.41, 535.01, 535.11, 535.31, 535.41, 535.51, 535.61, 537.83, 537.84, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.x, 596.7, 599.7, 719.1x, 782.7, 784.7, 784.8, 786.3	I312, I609, I619, I621, I6200, I629, K648, K644, K648, I8501, I8511, R58, K226, K228, K250, K254, K256, K260, K262, K264, K266, K272, K274, K284, K2901, K2941, K2951, K2941, K2951, K2961, K2971, K2991, K2981, K31811, K3182, K5711, K5713, K5731, K5733, K661, K625, K5521, K920, K921, K922, N3289, R319, R310, R312, R311, M2500, M25019, M25029, M25039, M25049, M25059, M25069, M25073, M25076, M2508, M2500, R233, R040, R041, R042, R049
Prior stroke	433.01, 433.1, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 435.x, 436	G93.49, I67.89, G45.x, I63.x, I74.x

ICD-9-CM indicates International Classification of Diseases, Ninth Revision, Clinical Modifications; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modifications; NEC is not elsewhere classifiable.

Data Analyses

We compared the characteristics of patients who received oral anticoagulation from the VA with those who did not receive anticoagulation, using multivariable adjusted logistic regression analyses. Among Veterans with NVAF with documentation that they received anticoagulation within the VA, we compared the characteristics of those who received a

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Table 2. Patient-Level Factors Associated With the Receipt of Anticoagulation Therapy From the Veterans Health Administration Among Patients With Non-Valvular Atrial Fibrillation, 2007 to 2016

Characteristic	Received Anticoagulation From VA (n=405 516)	Did Not Receive Anticoagulation From VA (n=581 857)	Adjusted Odds Ratio*
Age (mean), y	75.7	77.1	1.00 (1.00–1.00)
Age, y			
<65	12	13	REF
65 to 74	35	28	1.26 (1.23–1.29)
75 to 84	30	29	1.15 (1.11–1.19)
≥85	23	31	0.89 (0.85–0.93)
Sex			
Women	2	2	REF
Men	98	98	1.19 (1.15–1.23)
Race			
White	85	86	REF
Black	9	8	1.09 (1.08–1.11)
Other	6	6	0.98 (0.96–1)
Geographic region			
Northeast	15	19	REF
Midwest	25	24	1.23 (1.21–1.25)
West (including Pacific)	21	20	1.26 (1.24–1.28)
South	39	38	1.16 (1.14–1.18)
Body mass index, kg/m^2			
<25	24	28	REF
25 to 29.9	31	31	1.03 (1.02–1.05)
30 to 34.9	22	18	1.06 (1.04–1.08)
≥35	19	12	1.11 (1.07–1.14)
Comorbid conditions†			
Heart failure	20	17	1.19 (1.17–1.2)
Hypertension	70	68	0.97 (0.96–0.99)
Vascular disease	15	17	0.80 (0.79–0.81)
Diabetes mellitus	40	38	0.86 (0.85–0.87)
Prior bleeding	5	6	0.83 (0.81–0.84)
Prior stroke	9	7	1.30 (1.27–1.33)
CHA_2DS_2-VASc Score, %			
0 to 1	9	9	0.79 (0.77–0.82)
2 to 4	75	73	1.04 (1.02–1.07)
5 to 9	14	14	REF
eGFR categories (%), in units of mL/min per 1.73 m^2			
<30	8	9	1.08 (1.06–1.1)
30 to 44	14	15	1.13 (1.11–1.15)
45 to 59	17	17	1.11 (1.1–1.13)
≥60	59	50	REF
Elixhauser comorbidities			
0 to 2	28	29	REF
3 to 4	35	34	0.96 (0.94–0.97)
≥5	31	29	0.92 (0.91–0.94)

Percentages are shown except as otherwise noted. All statistical comparisons in the table are significant at the $P<0.001$ level. eGFR indicates estimated glomerular filtration; VA, Veterans Health Administration.

*Odds ratio for receiving anticoagulation from Veterans Health Administration vs not receiving. Adjusted for all other variables in the table.

†For each condition, the reference category is patients without the condition.

DOAC with those who received warfarin with similar analytic approaches. We also calculated temporal trends with regard to the receipt of new (incident) anticoagulants in patients with newly diagnosed NVAF and prevalent use (across the entire population of patients with prevalent NVAF). All analyses were conducted using SAS, version 9.4 (SAS Corporation, Cary, NC).

Results

Study Population Characteristics

During the decade-long period under study (2007–2016), there were a total of 987 373 VA patients with a diagnosis of NVAF (Table 2). The mean age of these patients was 76 years, 98% were men, and 86% were white. The majority of patients (88%) had a CHADS-VASc score of ≥2, corresponding to an appreciable risk of stroke.

Trends in Anticoagulation Use

Overall, during the 10-year period under study, 47% of patients with NVAF received some form of anticoagulation therapy from the VA (Figure 1). The proportion who were treated with anticoagulation was 56% in our initial study year of 2007, declined during the middle of the study period (2012: 44%), and by 2016 the proportion who were treated with anticoagulation had increased to 51%.

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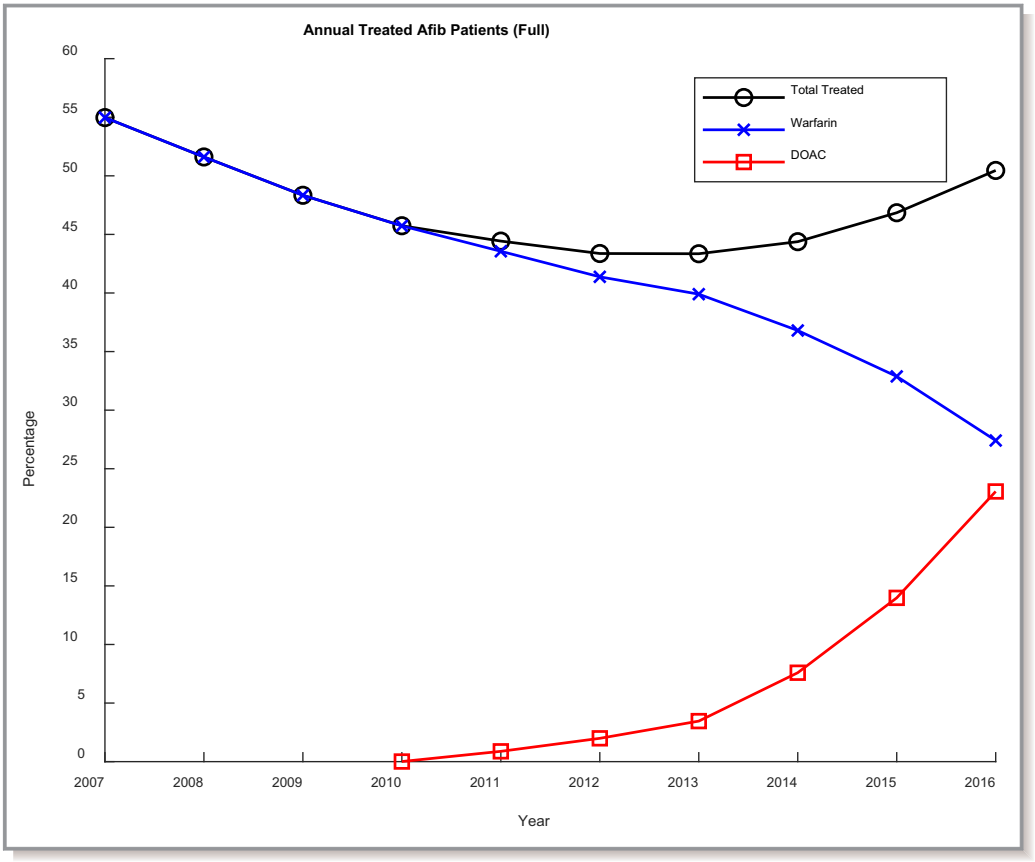

Figure 1. Trends in the receipt of direct oral anticoagulants (DOAC) and warfarin in patients with prevalent non-valvular atrial fibrillation (AFib) in the Veterans Health Administration.

Patient Characteristics Associated With the Receipt of Anticoagulation

Several patient-level characteristics were associated with the receipt of anticoagulation (Table 2). In the multivariable adjusted model, patients with heart failure or prior stroke were more likely to receive anticoagulation than those without these conditions, whereas patients with diabetes mellitus or prior bleeding were less likely to receive anticoagulation than respective comparison groups. Patients with a CHADS-VASc score of 0 to 1, for whom anticoagulation is generally not recommended, were less likely to receive anticoagulation (adjusted odds ratio [AOR], 0.79). Patients with impaired renal function, as compared with those with normal renal function, were slightly more likely to receive anticoagulation.

Trends in the Use of Direct Acting Oral Anticoagulants Versus Warfarin

All analyses from this point on will focus on the subset of patients with NVAF who received a first prescription for an oral anticoagulant from the VA between 2011 and 2016, which is the period when DOACs were in use—a total of 45 753 unique patients (Table 3). During this period, 81% of patients who received anticoagulation from the VA were treated with warfarin, while the remainder received a DOAC (Figure 1). The proportion of anticoagulation recipients who received a DOAC was only 2% in 2011; by 2016, it had increased to 45%. For new prescriptions, the trend was even more pronounced. In 2011, only 4% of new prescriptions for anticoagulants in the VA were for a DOAC; this proportion increased to 67% in 2016.

Patient Characteristics Associated With the Receipt of Direct Acting Oral Anticoagulants Versus Warfarin

We examined the patient sociodemographic and clinical characteristics associated with the receipt of a DOAC versus warfarin, among all patients who received oral anticoagulation from the VA for NVAF. This analysis was limited to the 45 753 patients who received a first prescription for an oral anticoagulant from the VA during 2016, the final year of our study (Table 3). Age and sex were not important determinants of receiving a DOAC as opposed to warfarin. DOAC use varied by region, with the highest rate of use in the Northeast and

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Table 3. Patient-Level Factors Associated With Receiving a DOAC From the Veterans Health Administration for Atrial Fibrillation During 2016, as Compared With Receiving Warfarin, Among Those Who Received an Initial Prescription for an Oral Anticoagulant During That Year

Characteristic	Received a DOAC (n=30 733)	Received Warfarin (n=15 020)	Adjusted Odds Ratio* to Receive a DOAC
Age (mean), y	73.7	72.2	…
Age (y) (%)			
<65	14	18	REF
65 to 74	43	46	0.96 (0.87–1.05)
75 to 84	28	24	1.00 (0.85–1.17)
≥85	15	12	1.13 (0.91–1.40)
Men, %	98	98	0.94 (0.79–1.11)
Race			
White	87	83	REF
Black	8	11	0.86 (0.80–0.93)
Other	5	6	0.97 (0.88–1.06)
Geographic region			
Northeast	16	14	REF
Midwest	24	26	0.8 (0.75–0.86)
West (including Pacific)	21	21	0.85 (0.79–0.92)
South	39	39	0.93 (0.87–0.99)
BMI, kg/m^2			
<25	19	19	REF
25 to 29.9	33	29	1.09 (1.01–1.17)
30 to 34.9	26	25	1.07 (0.97–1.18)
>35	20	24	1.05 (0.91–1.2)
Key comorbid conditions†			
Heart failure	16	23	0.82 (0.77–0.88)
Hypertension	74	76	1.22 (1.14–1.3)
Vascular disease	28	35	0.90 (0.85–0.95)
Diabetes mellitus	66	70	0.96 (0.91–1.02)
Prior bleeding	5	7	0.77 (0.71–0.84)
Stroke	6	9	0.74 (0.67–0.81)
CHA_2DS_2-VASc Score, %			
0 to 1	9	8	1.02 (0.87–1.19)
2 to 4	71	66	0.99 (0.91–1.08)
5 to 9	18	23	REF
eGFR categories (%), in units of mL/min per 1.73 m^2			
<30	2	9	0.20 (0.18–0.23)
30 to 44	9	9	0.70 (0.64–0.76)
45 to 59	16	14	0.86 (0.81–0.92)
≥60	71	67	REF
Elixhauser comorbidities			
0 to 2	27	22	REF
3 to 4	37	32	0.94 (0.88–1.00)
≥5	28	41	0.68 (0.63–0.73)

Percentages are shown except as otherwise noted. BMI indicates body mass index; DOAC indicated direct-acting oral anticoagulants; eGFR, estimated glomerular filtration.
*Adjusted for all the other variables in the table.
†For each condition, the reference category is patients without the condition.

the lowest in the Midwest (adjusted odds ratio, or AOR, 0.80 compared with the Northeast). Patients of black race were less likely to receive a DOAC than those of white race (AOR=0.86). Patients with heart failure, prior bleeding, and prior stroke were less likely to receive a DOAC than those without these conditions (AOR=0.82, 0.77, and 0.74, respectively). Patients with >2 Elixhauser comorbid conditions were less likely to receive a DOAC; for example, those with ≥5 conditions had an AOR of 0.68 compared with those with ≤2 conditions. Finally, impaired kidney function was associated with a lower likelihood of DOAC use, a with larger effect sizes as the degree of kidney function became more severe (AOR for estimated glomerular filtration rate <30=0.20, compared with estimated glomerular filtration rate ≥60).

Trends in DOAC Use

We examined trends in DOAC use across the VA system between 2011 and 2016 (Figure 2). Dabigatran accounted for all of the DOAC prescriptions in 2010 and 2011, as it was the only DOAC available. Beginning in 2012, about the time of their release to market, apixaban and rivaroxaban began to be prescribed and the proportion of dabigatran-treated patients declined. By 2016, 53% of new DOAC prescriptions were for apixaban, 28% were for rivaroxaban, and only 20% were for dabigatran.

Discussion

The results of this large observational study suggest changing practice patterns in the types of anticoagulant therapies used for stroke prevention in patients with new onset or long standing NVAF during the years under study. Although

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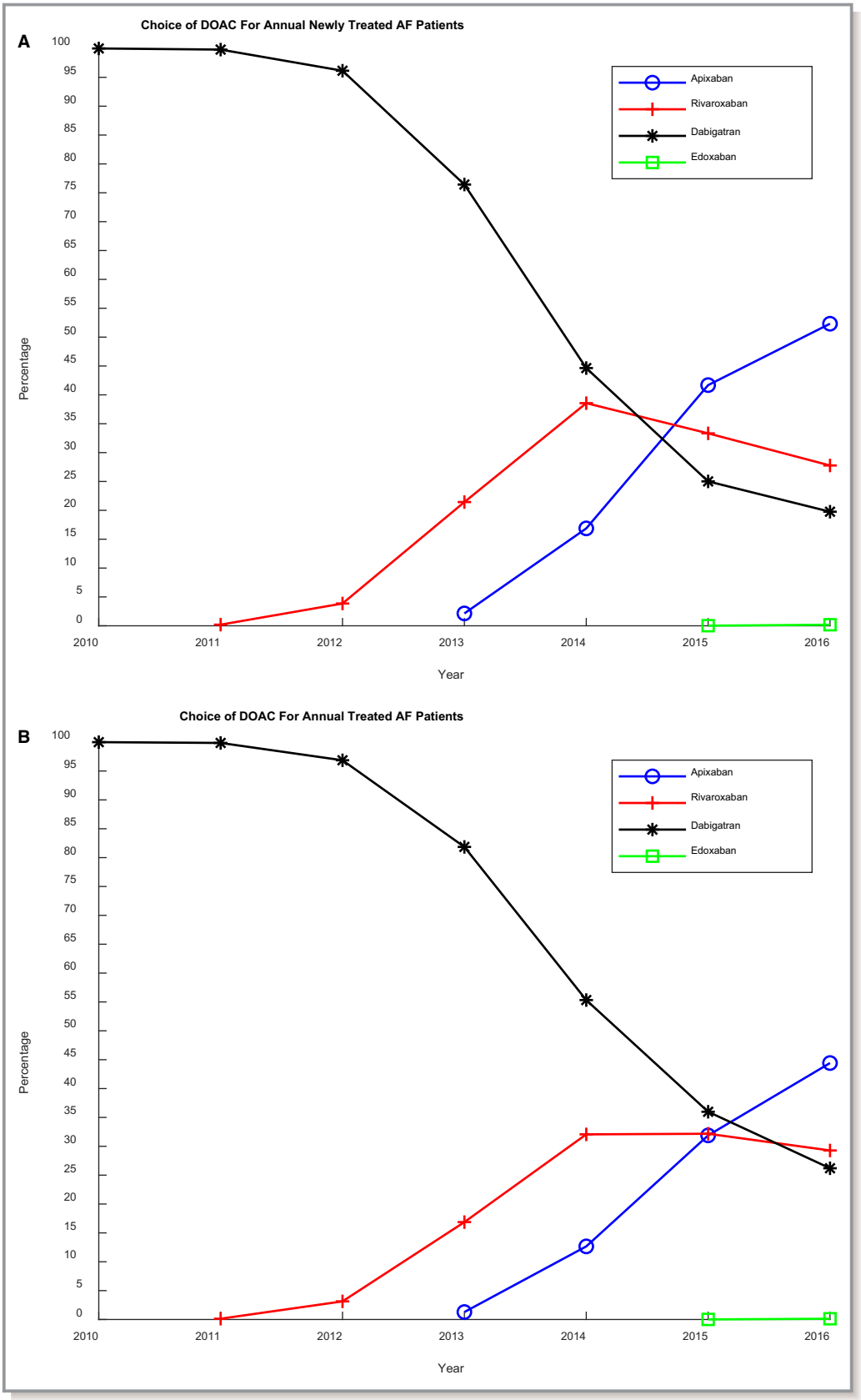

Figure 2. Trends in which medication was selected, among all recipients of direct oral anticoagulants (DOAC) for non-valvular atrial fibrillation (AF) in the Veterans Health Administration. **A**, Among new prescriptions (incident), (**B**) Among all prescriptions (prevalent).

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warfarin therapy remained the most commonly used oral anticoagulant for patients with NVAF throughout the study period, there was a progressive increase in the use of DOACs over time. By 2016, although the prevalent rate of warfarin use remained higher than for all DOACs combined, the proportion of new anticoagulation prescriptions for a DOAC was 67%. These findings are consistent with recent US registry data showing that more than half of patients with NVAF receiving anticoagulation are treated with warfarin, but that the majority of new prescriptions are for a DOAC.[5]

One of the promises of DOACs has been to expand the number of patients with NVAF who are willing and able to receive anticoagulation therapy for stroke prevention. Similar to the results of previous studies,[5] we did not detect a meaningful change in the percentage of patients with NVAF who received anticoagulation after the introduction of DOACs. This percentage was 56% in 2007, our first year of data, and 51% in 2016, 5 years after DOACs first became available in the VA. These data suggest that DOACs have not increased the overall proportion of anticoagulation-eligible patients who actually received therapy for stroke prevention in AF, even in a system that provides equal access to care and limits copayments to no more than $9 per medication per month—features that would tend to encourage greater use of these agents, because patients are largely shielded from out-of-pocket costs. This finding suggests that factors other than out-of-pocket drug costs may more strongly influence anticoagulation decision-making than has previously been appreciated.

In fact, there is a rich literature about the reasons why approximately half of patients with NVAF do not receive anticoagulation therapy. One particularly illustrative chart-review study from the pre-DOAC era[24] found that 55% of patients with NVAF were receiving anticoagulation, a proportion consistent with the published literature.[14] Of the remainder, most had documented reasons for not receiving anticoagulation: most commonly, gastrointestinal bleed, an expectation that atrial fibrillation would be transient, and increased risk of falls. Only 7.1% of the patients lacked a documented reason for omitting anticoagulation. It is worth noting that patient refusal to take warfarin because of inconvenience was not a prominent reason for its omission in this study. Therefore, it may not be terribly surprising that the advent of a medication that markedly decreases inconvenience may not have increased the proportion of patients with NVAF who receive anticoagulation.

Our study also examined some of the patient-level variables that may influence who receives a DOAC versus warfarin. Some of the predictors of receiving a DOAC in our analyses seem evidence based. For example, we found markedly lower rates of use of DOACs among NVAF patients with increasing levels of renal impairment. DOACs are relatively or absolutely contraindicated in the presence of significant chronic renal insufficiency or end-stage renal disease.[25–27] Other findings, such as a lower likelihood of receiving DOAC therapy among those with prior stroke or prior bleeding, and especially among patients with a greater number of comorbid conditions, are less evidence-based, although they are in agreement with the findings of previous observational studies.[4–7,28–30] Finally, while the effect size is rather small, it is noteworthy that black patients were less likely than whites to receive DOACs, even after controlling for covariates such as kidney function, and even in the context of a system that provides equal access to care, central guidance on how to use medications, and low copayments. Several previous studies in non-VA settings have also shown that white patients are more likely to receive a DOAC.[28–31] Finding this disparity in the VA system, where access and cost issues are largely eliminated, suggests some other provider or patient predisposition against the use of DOACs.

This study has several important strengths, including the size and detail of the database, and the availability of a decade of longitudinal data in which we were able to examine trends in the receipt of different anticoagulant therapies used for the prevention of stroke in patients with AF. However, this study also has several limitations that need be kept in mind in the interpretation of the present results. Based on our prior work,[32] we expect that we might have misspecified the anticoagulation status of 10% of patients who received *warfarin* outside of the VA system. In contrast, for patients eligible for VA benefits, receiving a *DOAC* outside the VA would be unusual, since VA copayments for medications are limited to no more than $9/month,[18] whereas out-of-pocket payments for VA patients receiving DOACs outside the VA system are often ≥$100/month.[6] Another potential limitation is that our study does not contain a counterfactual. While we did not find that the proportion of patients receiving anticoagulation increased in the VA after the introduction of DOACs, we cannot know for sure if that proportion would have been still lower had the DOACs not become available during this period.

Another limitation is that VA patients are mostly men and have a high burden of comorbid illness and social need. However, our study used data from the nation's largest integrated healthcare system to examine trends in DOAC use and uptake in a system that sharply limits the size of copayments. Thus, our results may be applicable in similar situations, such as nations that provide a high level of medical benefits.

Finally, our estimates for patient-level predictors of receiving a DOAC, as opposed to warfarin, used all new anticoagulant prescriptions from 2016. We used this year as it was the latest year of data available to us, and because the trend line of DOAC prescriptions (Figure 1) was beginning to level off by this time. However, we acknowledge that patterns of anticoagulant prescribing had not completely stabilized by

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2016, and indeed may not have stabilized to date. Therefore, it is unavoidable that the estimates in Table 3 reflect 2016 patterns of practice, and may not precisely reflect what would have been found in earlier or later years. In addition, estimates based on only 1 year of data may be less robust, although the sample size of >45 000 for this analysis is likely sufficient to ensure stable estimates.

Conclusion

Our study does not suggest that the introduction of DOACs led to an increase in the proportion of patients with NVAF receiving anticoagulation in the VA setting. In the VA, DOACs appear to be given preferentially to patients who have fewer comorbid conditions, who do not have a history of prior bleeding or stroke, and who are white. These findings run counter to what best practices might suggest as ideal, including recently released management guidelines for atrial fibrillation.[21] Almost a decade after the introduction of DOACs, we continue to use them rather haphazardly, even in a setting where their direct cost to patients is sharply curtailed. Our results suggest a need to rationalize our use of DOACs to maximize their benefit.

Author Contributions

Study design: Rose, Goldberg, McManus, Kapoor, Yu; analysis and interpretation: all authors; data manipulation and curation, statistical programming: Wang, Liu; drafted the manuscript: Rose, Goldberg; revised the manuscript for important intellectual content: all authors; approved the final manuscript: all authors; secured funding: Yu; study supervision: Yu.

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