

Group-Based Trajectory Modeling A Retrospective Study To Assess Adherence To Direct Oral Anticoagulants or Warfarin Among Atrial Fibrillation Patients and Comorbid Hypertension, Diabetes Mellitus, and Hyperlipidemia: A Retrospective Study.

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Research Article

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Abstract

Background

Poor adherence to oral anticoagulants is a significant problem in atrial fibrillation (AF), especially among patients with comorbid hypertension (HTN), diabetes mellitus (DM), and hyperlipidemia as it increases the risk for cardiac and thromboembolic events. Group-based trajectory modeling (GBTM) has been used to depict longitudinal patterns of adherence.

Aim

This primary objective was to describe adherence trajectory patterns of direct oral anticoagulants (DOACs) or warfarin among AF patients with HTN, DM, and hyperlipidemia using GBTM. The secondary objective was to report the clinical outcomes and concomitant drug use among DOAC/warfarin cohort

Method

This retrospective study was conducted among continuously enrolled Medicare Advantage Plan from January 2016-December 2019. AF patients were included in this study if they had comorbid HTN, DM, and hyperlipidemia with at least one pharmacy claim for warfarin/DOAC prescription. Monthly adherence to DOAC/warfarin was measured using proportion of days covered (PDC) and then modeled in a logistic GBTM to describe patterns of adherence. Patient's demographic, clinical characteristics, and concomitant use of DOACs/warfarin with CYP3A4,P-gp inhibitors were measured and compared across trajectories.

Results

Among 317 patients, 137 (59.62%) and 79 (24.92%) were DOAC, and warfarin users, respectively. The trajectory model for DOACs included gradual decline in adherence (GD, 40.4%), adherent (38.8%), and rapid decline (RD, 20.8%). The trajectories for warfarin adherence included gradual decline (GD, 18.9%), adherence (59.4%), and gaps in adherence (GA, 21.7%).

Conclusion

Adherence to oral anticoagulants is suboptimal. Interventions tailored according to past adherence trajectories may be effective in improving patient's adherence.

Impact Of Findings On Practice Statements

- At 1 year, adherence to DOACs/warfarin was suboptimal among multimorbid AF patients.

- Increased comorbidity burden and poor adherence resulted in increased the rates of stroke, thromboembolic events, cardiovascular events, and renal outcomes.
- Use of potentially interacting medications like P-gp/CYP34A with DOACs would increase the bleeding events and hence clinicians should consider prescribe alternative medications.

Introduction

Medication adherence is the extent to which the person adheres to the health care provider's recommendations for taking medications[1]. Poor adherence is a "silent epidemic," contributing to 21-37% of preventable adverse drug events[2]. Suboptimal adherence to oral anticoagulants like direct oral anticoagulants (DOACs) and warfarin is a major concern in atrial fibrillation (AF) patients. Perceived benefits of taking oral anticoagulants on a daily basis may not be apparent to asymptomatic AF patients resulting in suboptimal adherence[3] and worse clinical outcomes.

AF is predominantly seen in elderly with multiple comorbidities like hypertension (HTN), diabetes mellitus (DM), and hyperlipidemia. Approximately two-thirds of patients from the Phase III of the GLORIA-AF Registry reported at least three comorbidities[4]. HTN, hyperlipemia, and DM are the most widely reported cardiometabolic comorbidities in AF patients[5]. The presence of HTN, DM, and hyperlipidemia could further potentiate the risk of major adverse cardiac events and thromboembolic events among AF patients[6]. Furthermore, the prevalence of coronary revascularization, cardiac and all-cause mortality were found to be considerably higher among AF patients with HTN, DM, and hyperlipidemia than AF patients without these comorbidities[6]. Multimorbidity in AF patients also increases the healthcare resource utilization and economic costs[7].

Polypharmacy among multimorbid AF patients makes them vulnerable to clinically relevant potential drug-drug interactions. P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4) inhibitors increases the risk of bleeding events and hospitalization among AF patients when they are administered with DOACs or warfarin[8]. If DOAC users are concomitantly ≥ 2 interacting drugs, then it increases the odds of major bleeding by 4 times[9]. Hence the P-gp and CYP3A4 should be used with caution among oral anticoagulant users with comorbidities.

In clinical settings, pharmacy refill data has been used to estimate patient compliance[10]. By simplifying the longitudinal pharmacy refill data into simple summary figures, patients who may benefit from medication adherence interventions can be identified. However, the reduction in complexity results in information loss, especially regarding the patterns of adherence behavior. The proportion of days covered (PDC) reduces complexity and fail to account for the dynamic nature of adherence, resulting in an inability to distinguish patients with different initiation, implementation, and persistence behavior patterns[10]. The Group-Based Trajectory Model (GBTM) is a newer model used to measure adherence, and it provides two distinct advantages: first, its ability to identify groups of patients with similar prescription refill behavior patterns and intuitively display them, thereby allowing the potential tailoring of adherence interventions to patients which may enhance intervention effectiveness. Second, it defines the

trajectory of medication refill behavior over time, revealing a pattern of medication adherence for each group[10]. There have been several studies showing that GBTM is a better adherence indicator than PDC[10, 11].

The primary objective of this study was to develop GBTM for identifying the adherence trajectories of DOAC/warfarin among AF patients with HTN, DM, and hyperlipidemia. The secondary objective was to report the clinical outcomes and concomitant drug use among DOAC/warfarin cohort.

Ethics Approval

This study was approved by the institutional review board at the University of Houston.

Method

Study design and data source

A retrospective observational study was conducted using the Texas Medicare Advantage Plan database from January 2016-December 2019. For this analysis, membership files, member summary files, institutional claims, professional claims, and pharmacy files were used. Patient demographics and CMS risk scores were obtained from the membership and member summary files. Inpatient diagnostic information in the form of ICD-10 codes and outpatient encounters in the form of ICD-10 codes were identified from institutional and professional claims. Medication identifying information, date of service, quantity dispensed, days' supply, and dosing information were obtained from the pharmacy claims.

Patients were identified from July 2016-December 2017. Patients with a warfarin/DOAC prescription were identified one year after the patient identification period. The first date of warfarin or DOAC prescription was defined as the index date. All the demographic and clinical characteristics of the study population were captured six months before the index date (baseline period).

The baseline clinical and demographic variables included in the study were age, gender, low-income subsidy indicator (LIS), stroke risk score (CHA₂DS₂-VASc score), emergency room visits, prior hospitalization, use of antiplatelet agents, antiarrhythmic agents, use of NSAIDs, and mean CMS risk score.

Inclusion and exclusion criteria

The study population included adults ≥ 18 years. Patients diagnosed with paroxysmal, persistent, permanent AF, comorbid HTN, DM, and hyperlipidemia were included in this study. Patients had to be continuously enrolled during the entire study period. Patients should have at least a prescription refill for warfarin or any DOAC, which is comprised of dabigatran 110 mg, rivaroxaban 20mg, or apixaban 5mg. No patients had a prescription refill for edoxaban, and hence they were omitted. Patients who switched

from warfarin to any DOAC or vice versa were excluded from the study. Patients who had dementia during the baseline period were excluded.

Measurement of adherence

Patients with a prescription claim for warfarin/DOAC were followed up for one year after the index date to evaluate the adherence. During the 12-month follow-up period, PDC was calculated separately for each month, accounting for overlapping refills. Based on the PDC for each month, patients with $PDC \geq 0.80$ were considered adherent, while patients with $PDC < 0.80$ were considered non-adherent. These 12 binary indicators of warfarin/DOAC adherence were then modeled in a logistic group-based trajectory model. (PROC TRAJ, a downloadable add-on package to SAS version 9.4 [SAS Institute, Cary, NC]). The model parameters were estimated using maximum likelihood estimates. Two-five adherence groups were estimated using the second-order polynomial function of time. The final trajectory model was selected based on the Bayesian information criterion (BIC) value, clinical relevance, and minimum sample size of 5%[11].

Analysis plan

Baseline and clinical characteristics were compared by different trajectories of the final model using Fischer tests and ANOVA. Thromboembolic complications like stroke, transient ischemic attack, bleeding events, cardiovascular events like myocardial infarction, heart failure, renal disorder and dementia were recorded as frequencies and percentage. All the clinical outcomes were measured are the index date. The potential drug interaction of DOACs/warfarin with CYP3A4,P-gp inhibitors were given as frequencies and percentages. All statistical analyses were carried out using SAS 9.4 (SAS Institute, Cary, NC) at an a priori significance level of 0.05.

Results

The study population included 317 patients with AF, HTN, DM, and dyslipidemia. Among them, 137 (59.62%) patients were DOAC users, and 79 (24.92%) patients were warfarin users. Approximately fifty percent of DOAC users were females above the age of 66 (89.78%). Approximately one-fifth of the DOAC users had a CHA2DS2VASc score of 6 or more than 6 (20.44%). The mean baseline PDC of the DOAC cohort was 0.58 (± 0.29). The warfarin users were primarily comprised of females (58.23%), with a stroke risk of 5 or less than 5 (81.01%) and had no LIS (74.68%). The mean baseline PDC of warfarin users was 0.76 (± 0.24).

Adherence trajectories of DOACs/warfarin

Based on the Bayesian criteria, clinical relevance, and membership requirement, three distinct adherence trajectories were selected for both the DOAC and warfarin groups. The trajectory model for DOACs included group 1 as patients with gradual decline to DOAC adherence over time (GD, 40.4%); group 2 as adherent to DOACs (38.8%); group 3 as the rapid decline in adherence to DOACs (RD, 20.8%) (Figure 1).

The trajectories for warfarin adherence included group 1 as GD (18.9%), group 2 as adherence (59.4%), group 3 as gaps in adherence to warfarin (GA, 21.7%). Significantly more patients were in the warfarin adherence trajectory than the DOAC adherence trajectory (59.4% vs. 38.8%; $p=0.001$) (Figure 2).

Bivariate analysis of the adherence trajectories of DOACs/warfarin

Among the DOAC group, the mean baseline PDC in the RD (0.13), GD (0.41), adherent (0.83) was significantly different ($p<0.0001$). The three DOAC trajectories were significantly different for LIS ($p=0.005$). Furthermore, nearly two-thirds of patients from the adherence trajectory had a LIS. A significant difference in the use of antiplatelet agents among the three adherence trajectories was observed ($p=0.04$). The patients more commonly used antiplatelet agents in the RD than GD and adherent trajectory. The use of NSAID was significantly different across the three trajectory groups ($p=0.02$) (Table 1).

Table 1
Basic sociodemographic and clinic characteristics of direct oral anticoagulants by trajectory

Variables	Total Patients (N=137)	Rapid Decline (N=29; 21.2%)	Gradual Decline (N=55; 40.2%)	Perfect Adherence (N=53; 38.7%)	P value
Mean baseline PDC (SD)	0.58 (0.2)	0.13 (0.1)	0.41 (0.1)	0.83 (0.1)	<0.0001*
Sex, n (%)					
Male	67 (48.9)	12 (41.3)	23 (41.8)	32 (60.3)	0.100
Female	70 (51.0)	17 (58.6)	32 (58.2)	21 (39.6)	
Age group					
Less than 65	14 (10.2)	3 (10.3)	7 (12.7)	4 (7.5)	
65-75 years	64 (46.7)	15 (51.7)	28 (50.9)	21 (39.6)	0.460
≥76 years	59 (43.0)	11 (37.93)	20 (36.3)	28 (52.8)	
CHA2DS2VASc					
=< 5	109 (79.56)	24 (82.76)	45 (81.82)	40 (75.4)	
>= 6	28 (20.44)	5 (17.24)	10 (18.2)	13 (24.5)	0.680
ER visits					
No	130 (94.9)	27 (93.1)	52 (94.5)	51 (96.2)	
Yes	7 (5.1)	2 (6.9)	3 (5.45)	2 (3.7)	0.880
Prior Hospitalization					
No	116 (84.6)	25 (86.2)	42 (76.3)	49 (92.4)	0.060
Yes	21 (15.3)	4 (13.7)	13 (23.6)	4 (7.5)	
Mean Risk score (SD)	1.708 (0.8)	1.6 (0.9)	1.662 (0.9)	1.815 (0.7)	0.490
LIS					
No	76 (55.4)	22 (75.8)	33 (60)	21 (39.6)	0.005*
Yes	61 (44.5)	7 (24.1)	22 (40)	32 (60.3)	
Antiplatelet agents					

PDC: proportion of days covered; CHA2DS2VASc: stroke risk score; ER visits: emergency room visits; LIS: low-income subsidy; NSIADs: non-steroidal anti-inflammatory drugs. * Indicates significance

Variables	Total Patients (N=137)	Rapid Decline (N=29; 21.2%)	Gradual Decline (N=55; 40.2%)	Perfect Adherence (N=53; 38.7%)	P value
No	118 (86.1)	21 (72.4)	51 (92.7)	46 (86.7)	
Yes	19 (13.8)	8 (27.5)	4 (7.27)	7 (13.2)	0.041*
Antiarrhythmic agents					
No	101 (73.7)	20 (68.9)	45 (81.8)	36 (67.9)	
Yes	36 (26.2)	9 (31.0)	10 (18.1)	17 (32.1)	0.201
NSAIDs					
No	115 (83.9)	22 (75.8)	43 (78.1)	50 (94.3)	
Yes	22 (16.0)	7 (24.1)	12 (21.8)	3 (2.2)	0.022*
PDC: proportion of days covered; CHA2DS2VASc: stroke risk score; ER visits: emergency room visits; LIS: low-income subsidy; NSAIDs: non-steroidal anti-inflammatory drugs. * Indicates significance					

For the warfarin group, the baseline PDC was significantly different across the three trajectory groups ($p < 0.0001$). There were more female patients in the GD group than GA and adherent groups. More patients from the GD trajectory were above 76 years as compared to GD and adherent trajectory. A predominant number of patients in the adherent trajectory did not have a LIS as compared to the GD and GA trajectory (Table 2).

Table 2
Basic sociodemographic and clinic characteristics of warfarin cohort by trajectory

Variables	Total Patients N=79	Rapid Decline N=16 (%)	Gaps in Adherence N=15 (%)	Perfect Adherence N=48 (%)	P value
Mean baseline PDC (SD)	0.767 (0.2)	0.66 (0.1)	0.16 (0.1)	0.91 (0.1)	<0.0001*
Sex					
Male	33 (41.7)	6 (37.5)	8 (53.3)	19 (39.5)	0.562
Female	46 (58.2)	10 (62.5)	7 (46.6)	29 (60.4)	
Age group					
Less than 65	11 (13.9)	3 (18.7)	3 (20)	5(10.4)	
65-75 years	35 (44.3)	4 (25)	6 (40)	25 (52.1)	0.331
More than 76 years	33 (41.7)	9 (56.2)	6 (40)	18(37.5)	
CHA2DS2VASc					
=< 5	64 (81.0)	13 (81.2)	13 (86.6)	38 (79.2)	0.921
>= 6	15 (18.9)	3 (18.7)	2 (13.3)	10 (20.8)	
ER visits					
No	78 (98.7)	16 (100)	15 (100)	47 (97.9)	1
Yes	1 (1.1)	0	0	1 (2.1)	
Prior Hospitalization					
No	73 (92.4)	14 (87.5)	13 (86.6)	46 (95.8)	0.268
Yes	6 (7.59)	2 (12.50)	2 (13.3)	2(4.1)	
Mean Risk score	1.79 (0.8)	1.68 (0.7)	1.76 (0.9)	2.00 (0.7)	0.540
LIS					
No	59 (74.6)	12 (75)	8 (53.3)	39 (81.2)	0.102
Yes	20 (25.3)	4 (25)	7(46.6)	9 (18.7)	
Antiplatelet agents					
No	68 (86.1)	13 (81.2)	13 (86.6)	42 (87.5)	0.892

PDC: proportion of days covered; CHA2DS2VASc: stroke risk score; ER visits: emergency room visits; LIS: low-income subsidy; NSIADs: non-steroidal anti-inflammatory drugs. * Indicates significance

Variables	Total Patients N=79	Rapid Decline N=16 (%)	Gaps in Adherence N=15 (%)	Perfect Adherence N=48 (%)	P value
Yes	11 (13.9)	3 (18.7)	2 (13.3)	6 (12.50)	
Antiarrhythmic agents					
No	67 (84.8)	14 (87.5)	13 (86.6)	40 (83.3)	1
Yes	12 (15.2)	2 (12.5)	2 (13.3)	8 (16.6)	
NSAIDs					
No	70 (88.6)	15 (93.7)	14 (93.3)	41 (93.3)	0.682
Yes	9 (11.4)	1 (6.3)	1 (6.6)	7 (14.6)	
PDC: proportion of days covered; CHA2DS2VASc: stroke risk score; ER visits: emergency room visits; LIS: low-income subsidy; NSIADs: non-steroidal anti-inflammatory drugs. * Indicates significance					

Clinical outcomes

In the DOAC arm, stroke was reported among 10 (7.30%) patients. Major and minor bleeding events occurred among 26 (18.97%) patients. Cardiovascular outcomes like myocardial infarction (MI) and heart failure (HF) occurred in 13 (9.48%) and 16 (11.67%) DOAC users, respectively. Twenty-six (18.97%) DOAC users reported renal disorders. Alzheimer's disease or dementia was reported among 6 (4.0%) DOAC users.

During follow-up, the 4 (5.06%) stroke events occurred in the warfarin cohort. Any major and minor bleeding was reported among 9 (11.39%) warfarin users. MI and HF occurred in 6 (7.60%) and 11 (13.9%) warfarin cohorts, respectively. Renal disorders were reported among 29 (36.70%) warfarin users. Significant differences in renal disorders were identified among the three trajectory groups (GD=12, adherence trajectory =10, GA=7; p=0.0002). Alzheimer's disease or dementia was recorded in 6 (7.59%) warfarin users.

P-glycoprotein (p-gp)/CYP3A4 inhibitor drugs concomitantly used with DOAC/warfarin

P-gp/CYP3A4 inhibitor drugs like amiodarone, diltiazem, and ketoconazole were co-administered with DOAC/warfarin. Of the DOAC cohort, 9 (6.56%) patients used amiodarone, 3 (2.18%) patients used diltiazem, and 3 (2.18%) patients used ketoconazole. Among warfarin users, 30 (37.97%) patients received amiodarone, 13 (16.45%) patients received diltiazem, and 4 (5.06%) patients received ketoconazole.

Discussion

Adherence trajectories of DOACs and warfarin

To date, this is the first study to evaluate the adherence trajectories to DOAC and warfarin among AF patients with HTN, DM, and hyperlipidemia. This study identified three distinct trajectories in DOAC (adherence trajectory, RD, and GD) and warfarin (adherence trajectory, RD, and GA) users. This study found consistently poorer adherence to DOACs than warfarin among AF patients with multimorbidity. Only 39% of DOAC users and 59.4% of warfarin users were adherent for 1 year. Adherence to DOACs and warfarin is lower than other study findings[12–15]. This difference in adherence may be due to increased comorbidity burden, CHA₂DS₂VASc ≥ 5 , and regimen complexity in this population[15, 16]. Furthermore, comorbidities like diabetes/HTN are associated with suboptimal adherence among AF patients [16]. Approximately 41% of DOAC users were identified to have a gradual decline in adherence. DOACs have a shorter half-life than warfarin, and hence nonadherence to DOACs will result in more significant consequences and worse clinical outcomes[17]. Ease of DOAC use and lack of frequent DOAC monitoring is considered to be advantageous over warfarin. However, in this study, this lack of monitoring may have impacted adherence. Evidence suggests that monitoring of AF patients for a longer duration improves adherence[18].

Use of concomitant medications in multimorbid AF patients

A higher disease burden among AF patients results in regimen complexity and predisposes them to poor adherence[19]. Inadequate control of INR values and permanent discontinuation of medications were documented among AF patients who were prescribed with a greater number of concomitant drugs[20]. In this study, all patients taking ≥ 4 concomitant medications, including their oral anticoagulant, could impact the risk-benefit profile of DOACs/warfarin. Evidence suggests that a number of concomitant medications are associated with increased stroke, bleeding events, and mortality[21]. Medication regimen complexity impacts the risk-to benefit profile adversely and further decreases the quality of life. Concomitant use of statins among AF reduces CV and all-cause mortality, stroke, intracranial hemorrhage, gastrointestinal hemorrhage, and reduces the risk of dementia[22, 23]. The antithrombotic effect is attributed to ability of statins to alter coagulation and inhibit platelet activation[24]. All the patients in this study had a cardiovascular benefit due to the concomitant use of statins. The drug-drug interactions in this study underscore the need for better pharmacovigilance to reduce the risk of adverse events among high-risk patients. Clinicians should consider prescribing medications that can be safely co-administered with DOACs/warfarin.

Clinical outcomes among multimorbid AF patients

Another major concern in this study is regarding the clinical outcomes among AF patients with multimorbidity. Suboptimal adherence to DOACs significantly increases the incidence of stroke among high stroke risk patients, which is consistent with this study findings[3, 13, 25]. Furthermore, the increased stroke in this study can be attributed to the elevated stroke risk scores and comorbid DM. DM among AF increases the likelihood of thrombus formation through oxidative stress, inflammation, and platelet activation[26]. In this population, bleeding episodes were higher among the DOAC users. Additionally, the

unadjusted analysis showed that the bleeding events were similar across the adherent and nonadherent patients. Hence, the use of warfarin/DOACs alone cannot fully explain the increased incidence of bleeding. Increased bleeding events that could not be attributed to warfarin/DOAC exposure may be due to comorbidity burden, increased CHA₂DS₂VASc scores, and concomitant use of potentially interacting medications[27]. Health care professionals should educate patients about symptoms of drug-drug interactions like bleeding and stroke/transient ischemic attack.

Increased risk of MI among DOAC users is in line with the evidence which suggests that warfarin may be beneficial to reduce the risk of MI[28, 29]. The presence of comorbid HTN and DM in this study may have resulted in increased adverse kidney outcomes among AF patients[26]. This study results are consistent with a prior study that reported warfarin users had more pronounced renal disorders than DOAC users[30, 31]. Elderly AF patients with HTN and DM have reduced glomerular filtration rate (GFR), which may justify the higher rates of renal disorder in this study[30]. Renal impairment among AF patients increases the thromboembolic and cardiovascular complications than AF patients without renal complications[32]. This study result highlights the need for more frequent monitoring of renal function among these high-risk patients with multimorbidity. Finally, the DOAC users appeared to have a lower risk of dementia compared to the warfarin users and is consistent with prior studies[33, 34]. This should be further investigated in future studies. The clinical outcome in the study highlights the need for optimal management of comorbidities.

Drug-drug interactions with DOACs and warfarin

There is a potential need to cautiously monitor DOAC/warfarin users who are prescribed NSAIDs and antiplatelet agents due to the increased bleeding risk[27, 35]. Clinicians may consider prescribing cyclooxygenase-2 (COX-2) over NSAIDs for pain management as it is associated with less bleeding risk. [36] Clinically relevant interactions occur with DOACs/warfarin when they inhibit or induce p-gp and CYP3A4 pathways. Amiodarone, diltiazem, and ketoconazole were the most frequently prescribed p-gp/CYP3A4 inhibitor medications that interact with DOACs/warfarin and increase plasma levels DOACs/warfarin[37]. Patients with AF had significantly higher rates of stroke[38], systemic embolism,[38] and mortality[39, 40] when they received amiodarone than AF patients who did not take amiodarone. Concurrent use of DOACs and amiodarone was associated with significant increase in bleeding events[37]. Furthermore, co-administration of amiodarone and warfarin increases the risk of stroke and systemic embolism[38]. Despite this evidence, more than one-third of warfarin patients were prescribed with amiodarone. Concurrent administration of DOACs and diltiazem to AF patients significantly increase the bleeding events[37]. Co-prescriptions of ketoconazole and DOACs increase bleeding events [37]. Given the safety concerns related to ketoconazole, clinicians are advised to carefully evaluate such concerns prior to prescribing.

Limitations

This was an exploratory study. Due to the limitations of sample size, there was a limited scope of carrying out regression analysis across different trajectories. Due to the lack of adequate power, the association between adherence and outcomes could not be carried out. This study was conducted among patients enrolled in the Texas Medicare Advantage plan which limits generalization.

Conclusions

Suboptimal adherence to oral anticoagulants in this study warranted the need for regular follow-ups to identify the barrier for poor adherence. Furthermore, tailored interventions based on past adherence trajectories may be developed to improve adherence. A recent study reported that a motivational interviewing intervention tailored by past adherence trajectories was effective in improving statin adherence[41]. Given the higher rates of nonadherence to DOACs/warfarin, future research should be carried out with larger sample size, identify the barriers associated with nonadherence and address them to improve and maintain adherence for a longer duration in AF patients with multimorbidity.

Clinical guidelines for AF patients should also focus on effective disease management among AF patients with multimorbidity like HTN, DM, and hyperlipidemia. Guidelines should aid providers in prioritizing treatment among multimorbid patients. Clinicians may consider designing care pathways around individual patient needs rather than their disease conditions. Healthcare professionals can deliver medication therapy management (MTM) services by identifying the clinical appropriateness of each medication, improving medication adherence by patient education[42], evaluating potential adverse effects related to concomitant medications, and further develop a plan to resolve the medication-related issues which could improve the clinical outcomes among AF patients[43].

Declarations

Conflict of interests

Authors have no conflicts of interest to disclose. Dr. Abughosh reports grants from Valeant, grants from Regeneron, and grants from Pfizer/BMS outside the submitted work

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Competing interests

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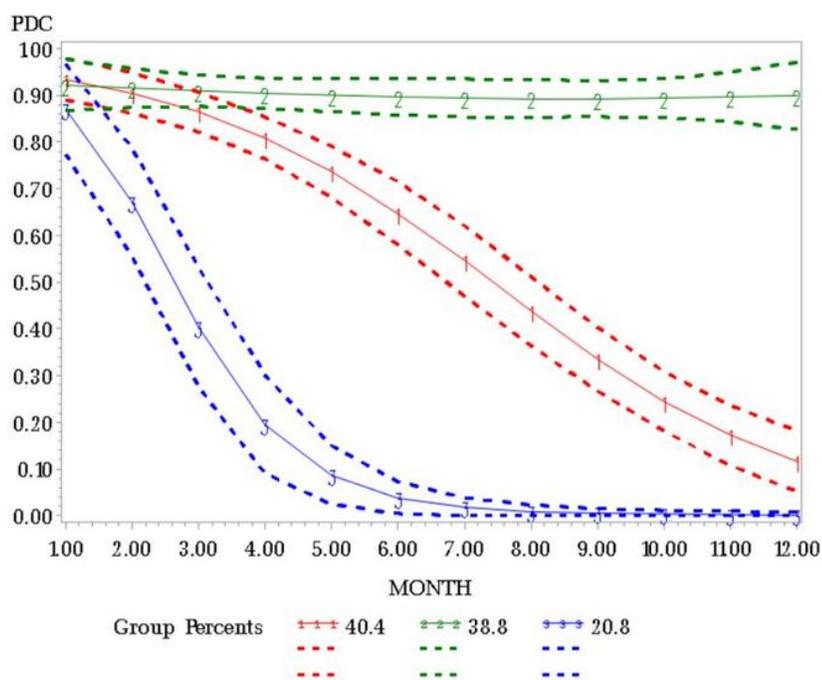
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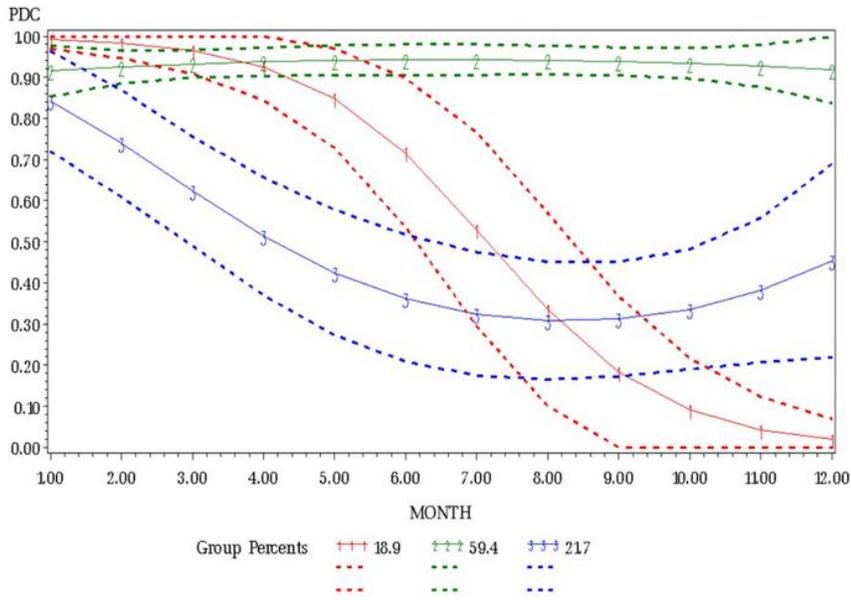
Figures



Trajectories	%
Adherent	38.8
Gradual Decline (GD)	40.4
Rapid decline (RD)	20.8

Figure 1

Trajectories of adherence to direct oral anticoagulants trajectory modeling



Trajectories	%
Adherent	59.4
Gradual Decline (GD)	18.9
Gaps in Adherence (GA)	21.7

Figure 2

Trajectories of adherence to warfarin