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ORIGINAL RESEARCH

Adherence and persistence to direct oral anticoagulants in atrial fibrillation: a population-based study

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ABSTRACT

Background Despite simpler regimens than vitamin K antagonists (VKAs) for stroke prevention in atrial fibrillation (AF), adherence (taking drugs as prescribed) and persistence (continuation of drugs) to direct oral anticoagulants are suboptimal, yet understudied in electronic health records (EHRs).

Objective We investigated (1) time trends at individual and system levels, and (2) the risk factors for and associations between adherence and persistence.

Methods In UK primary care EHR (The Health Information Network 2011–2016), we investigated adherence and persistence at 1 year for oral anticoagulants (OACs) in adults with incident AF. Baseline characteristics were analysed by OAC and adherence/persistence status. Risk factors for non-adherence and non-persistence were assessed using Cox and logistic regression. Patterns of adherence and persistence were analysed.

Results Among 36 652 individuals with incident AF, cardiovascular comorbidities (median CHA_2DS_2VASc[Congestive heart failure, Hypertension, Age≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category] 3) and polypharmacy (median number of drugs 6) were common. Adherence was 55.2% (95% CI 54.6 to 55.7), 51.2% (95% CI 50.6 to 51.8), 66.5% (95% CI 63.7 to 69.2), 63.1% (95% CI 61.8 to 64.4) and 64.7% (95% CI 63.2 to 66.1) for all OACs, VKA, dabigatran, rivaroxaban and apixaban. One-year persistence was 65.9% (95% CI 65.4 to 66.5), 63.4% (95% CI 62.8 to 64.0), 61.4% (95% CI 58.3 to 64.2), 72.3% (95% CI 70.9 to 73.7) and 78.7% (95% CI 77.1 to 80.1) for all OACs, VKA, dabigatran, rivaroxaban and apixaban. Risk of non-adherence and non-persistence increased over time at individual and system levels. Increasing comorbidity was associated with reduced risk of non-adherence and non-persistence across all OACs. Overall rates of 'primary non-adherence' (stopping after first prescription), 'non-adherent non-persistence' and 'persistent adherence' were 3.5%, 26.5% and 40.2%, differing across OACs.

Conclusions Adherence and persistence to OACs are low at 1 year with heterogeneity across drugs and over time at individual and system levels. Better understanding of contributory factors will inform interventions to improve adherence and persistence across OACs in individuals and populations.

INTRODUCTION

For 60 years, vitamin K antagonists (VKAs), mainly warfarin, dominated stroke prevention in atrial fibrillation (AF), the most common arrhythmia globally.[1 2] Successive approval of four direct oral anticoagulants (DOACs: dabigatran,[3] apixaban,[4] rivaroxaban[5] and edoxaban[6]) changed the landscape, with early adoption in guidelines[7 8] and quality improvement initiatives.[9] DOACs are often preferred over VKA due to reduced international normalised ratio (INR) monitoring, but only if OAC services are fully decommissioned and DOACs are taken appropriately. Paradoxically, removal of the need for INR monitoring also removes additional patient–clinician engagement that encourages adherence (taking drugs as prescribed) and persistence (continuation of therapy),[10] both pertinent to oral anticoagulants (OACs) with a lifelong therapeutic indication.

Despite its importance in the context of population ageing, declining cognitive function, multimorbidity and polypharmacy, adherence was unreported in trials of DOACs,[3–6] despite short half-lives, particularly dabigatran and apixaban which require dosing two times per day.[11] Reported trial persistence was highest for dabigatran (79.3% at low dose) and lowest for edoxaban (65.6% at high dose)[3–6] (online supplementary web table 1). All DOACs have proven efficacy compared with VKA, although at much lower time in therapeutic range (TTR) in trials than usual clinical practice, but 'head-to-head' DOAC trial comparisons are unlikely. However, several studies have shown suboptimal adherence and persistence for DOACs in different countries and settings, even compared with VKA, and effective interventions are lacking.[12–14] Underlying causes include factors at social, economic, health system, clinician and patient levels. Although all patient-level factors are not captured, electronic health records (EHRs) allow population-level studies of adherence and persistence together across all DOACs in the same data set, which are rare.[13]

Only one study to date has considered all metrics of drug utilisation ('initiation', 'implementation' and 'discontinuation') together rather than 'adherence' or 'persistence' in isolation[15] for OAC in AF.[13] Steps in drug utilisation may be described as the 'prescription-persistence cascade' (from

'recommendation' to 'persistence'/'continuation'), estimable from EHR. For OAC in AF, the steps are *'recommendation'* (eligible for OAC), *'initial prescription'* (≥1 OAC prescription), *'dispensing'* (no EHR data), *'initiation by patient'* (no EHR data), *'adherence'*/*'implementation'* (adherent to OAC) and *'persistence'*/*'continuation'* (persistent to OAC). Interaction between adherence and persistence is often overlooked, for example, 'persistent and non-adherent' (ie, continuing medications but not taking as prescribed) versus 'non-persistent and non-adherent' (ie, discontinued medications and also not taking as prescribed).

The UK has universal primary healthcare, enabling large-scale, representative data sets where uptake, adherence and persistence for different DOACs can be studied. We used The Health Improvement Network (THIN) database in the UK to investigate adherence and persistence for OACs in individuals with AF, focusing on (1) time trends since DOAC introduction at health system level and after initiation in individuals; (2) relative impact of sociodemographic and baseline risk factors and treatment characteristics; and (3) associations between adherence and persistence.

METHODS

The study conformed to the Strengthening the Reporting of Observational Studies in Epidemiology recommendations.[16]

Data source

The THIN database includes longitudinal, anonymised EHRs from over 500 UK general practices using Vision software (INPS, www.inps4.co.uk/), representative of the UK population.[17]

Study population

Our retrospective cohort included individuals aged ≥18 years with first-ever, non-valvular AF diagnosis between January 2011 and December 2016 and first prescription of VKA/DOAC on or after the date of AF diagnosis. The date of first prescription became the index date. For inclusion, patients needed ≥90 days of follow-up. Individuals with ≥1 prescription of VKA/DOAC were eligible for inclusion in adherence/persistence analyses. Exclusion criteria were taking OAC for other indications (eg, deep vein thrombosis and pulmonary embolism). Follow-up was until outcome event, death, the patient leaving the database or the most recent data upload.

Baseline covariates

Baseline factors were assessed: demographics (age, sex, Townsend Deprivation Index quintile level 1—the least deprived category), comorbidities (heart failure, hypertension, diabetes mellitus, stroke/transient ischaemic attack, vascular disease, liver disease, hypercholesterolaemia, ie, on statin and/or had hypercholesterolaemia), social history (alcohol misuse, smoking status) and drug history (aspirin, statin, blood pressure-lowering drugs, and mean number of drugs including OAC, prescribed in ≤365 days until, but not including, the episode start date). CHA_2DS_2VASc (Congestive heart failure, Hypertension, Age≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category[18]) and 'HASBLED-1' (rather than HASBLED (Hypertension,Abnormal renal/liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs or alcohol[19]), since INR and 'labile INR' were not available) scores were calculated from available variables and categorised based on current guidelines.

Outcomes

Outcomes were adherence to and persistence with OACs. Adherence was estimated by proportion of days covered (PDC) over the year following first prescription of VKA/DOAC, which more accurately reflects patient behaviour and treatment continuity than other adherence measures[20]:

$$\text{PDC} = \frac{\text{Number of days with drug supplied (up to maximum of 365)}}{\text{Number of days between first and (last+30 days) prescription or 365 days}*}$$

*(*whichever is shorter*)

Each prescription was assumed to last 30 days, unless a new prescription was issued within 30 days, in which case the original prescription's duration was assumed to equal the gap between the two prescriptions. Patients with only one OAC prescription were classed as 'missing' and not included in the estimation. Impact of varying PDC threshold to 70% and 90% was examined for all OACs. Adherence was defined as PDC >80% like previous studies[21] and produced more stable estimates. Individuals prescribed VKA/DOAC were deemed persistent until a prescription gap >90 days on that or an alternative OAC ('switch'), in which case they were non-persistent, or there was no further longitudinal data (in which case persistence status was unknown beyond that time). For each DOAC, proportion of switching to VKA or another DOAC was analysed over 12 months. Impact of varying prescription gaps to 60 and 120 days was examined for all OACs. Like previous studies,[22] the 90-day prescription gap was used, providing more stable estimates. As prescription gaps lengthened, persistence improved more with VKA than DOACs (online supplementary web table 1).

Statistical analysis

Baseline characteristics were analysed by OAC. If any OAC/DOAC group consisted of <100 individuals, sample size was deemed too low to undertake meaningful analysis. Persistence was estimated using Kaplan-Meier product-limit estimator. Crude persistence for different OACs was estimated through survival life tables (adopting different prescription gaps) and ascertaining the number and percentage (95% CI) of patients still in the study (ie, persistent or uncensored) after 1 year. After stratification by adherence/persistence status at 12 months, baseline characteristics were determined. χ^2 test and analysis of variance test were used for categorical and continuous covariates, respectively. Relative effects of OACs on non-adherence and non-persistence were modelled using univariable and multivariable logistic regression and Cox proportional hazard regression (simple and multiple), respectively. For multivariable analyses, we adjusted for date of first OAC prescription (relative to study start date), CHA_2DS_2VASc, HASBLED-1, Townsend Deprivation Index quintile and number of drugs. Optimal adjustments for CHA_2DS_2VASc, HASBLED-1, number of drugs and date of first OAC prescription were investigated using continuous variables (including potential quadratic effects) or clinically appropriate categorisation. Models were compared using Bayesian information criterion (BIC) and the optimal model chosen based on the lowest BIC. For Cox regression, the proportional hazards assumption was investigated by adding interactions with 'time in study'. Interactions were included if they improved the model (by BIC criterion). For non-adherence, a sensitivity analysis was performed in those who had ≥6 months' potential OAC coverage (ie, ≥6 months between date of first prescription and date of last prescription plus 30 days) and ≥12 months' OAC potential coverage to reduce potential bias in estimated adherence in short treatment periods, leading to an overestimate of PDC (online supplementary web tables 2a and 2b). For non-persistence, two sensitivity analyses were based around the

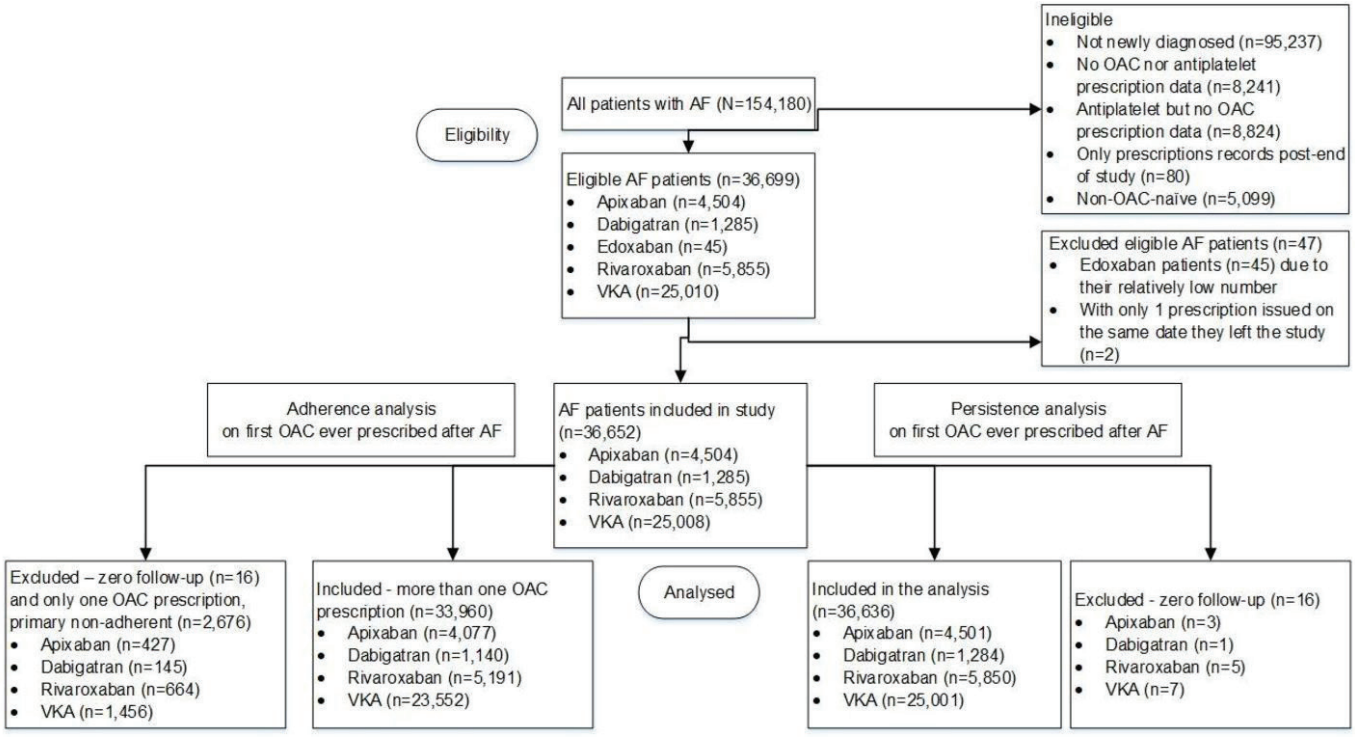

Figure 1 Flow diagram of study population for adherence and persistence analyses. AF, atrial fibrillation; OAC, oral anticoagulant; VKA, vitamin K antagonist.

chosen Cox regression model by (1) adding interactions (linear; linear and quadratic) between OAC and timing of first OAC prescription (relative to study initiation); and (2) reclassifying those switching to another OAC as censored (cessation of observation) rather than non-persistent to first OAC prescribed.

RESULTS

Among 4 354 740 individuals, 154 180 with AF were identified, of whom 36 652 met the inclusion criteria for analysis: VKA (n=25 008, 68.2%), dabigatran (n=1285, 3.5%), rivaroxaban (n=5855, 16.0%) and apixaban (n=4504, 12.3%) (figure 1). Major exclusions were no new AF diagnosis (n=95 237) and absence of OAC prescription data (n=17 065). Edoxaban was UK-approved in September 2015, leading to inadequate sample size for analysis (n=45) during the study period.

The study population had a mean age of 74.4 (SD 10.5) years and 45% were female. Cardiovascular comorbidities were common: hypertension (62.6%) and hypercholesterolaemia (71.8%), with a median CHA_2DS_2VASc of 3 (IQR 2–4). Polypharmacy was common (number of drugs: median 6, IQR 4–7). Individuals on dabigatran had lower CHA_2DS_2VASc scores, rates of hypertension and current smoking, with no other significant baseline differences across different OACs (table 1).

Adherence

Adherence was 55.2% (54.6–55.7) overall and 51.2% (50.6–51.8), 66.5% (63.7–69.2), 63.1% (61.8–64.4) and 64.7 (63.2–66.1) for VKA, dabigatran, rivaroxaban and apixaban, respectively (online supplementary web table 1).

In univariable analysis, the likelihood of non-adherence with DOACs was lower than with VKA (OR 0.53, 0.47–0.60; 0.61, 0.58–0.65; and 0.57, 0.54–0.61 for dabigatran, rivaroxaban and apixaban, respectively) (table 2 and online supplementary web table 2d). In multivariable analysis, the likelihood of non-adherence was similar for dabigatran (0.54, 0.48–0.62), but higher for rivaroxaban (0.76, 0.71–0.82) and apixaban (0.77, 0.71–0.84). Increasing comorbidity (by CHA_2DS_2VASc) was associated with decreased likelihood of non-adherence (1.00, 0.93–1.08; 0.94, 0.88–1.01; and 0.81, 0.74–0.89 for CHA_2DS_2VASc scores 2, 3–4 and 5–9, respectively, compared with CHA_2DS_2VASc scores 0–1), but not for HASBLED-1 score (0.98, 0.93–1.05 for HASBLED-1 scores ≥3, compared with HASBLED-1 scores 0–2). The number of drugs and Townsend quintile were not associated with non-adherence (table 2). Age ≥75 years, diabetes, female gender and anaemia were associated with reduced risk of non-adherence, while hypertension and vascular disease were associated with increased risk (online supplementary web table 2c). Non-adherence was non-linearly associated with time since introduction of DOACs, increasing for approximately 2 years (to early 2013) before starting to decrease, returning to its original level by early 2015 (online supplementary web figure 1a) and then dropping below its original level. Baseline characteristics by adherence status are shown in online supplementary web table 4. Online supplementary web table 2e illustrates no important differences in the effect of time since introduction of DOACs between different OACs (online supplementary web figure 1b). Sensitivity analysis in only those who had at least 6 or 12 months of OAC prescriptions showed little impact on relative non-adherence for dabigatran and VKA; however, estimated ORs for rivaroxaban and apixaban both decreased to 0.65 (for 12-month restriction) (online supplementary web tables 2a and 2b).

Persistence

One-year persistence was 65.9% (65.4–66.5) overall and 63.4% (62.8–64.0), 61.4% (58.3–64.2), 72.3% (70.9–73.7) and 78.7% (77.1–80.1) for VKA, dabigatran, rivaroxaban and apixaban, respectively. Persistence reduced over 3 years for all OACs and

Table 1 Baseline characteristics of study population

	Overall (N=36 652)	VKA (n=25 008)	Dabigatran (n=1285)	Rivaroxaban (n=5855)	Apixaban (n=4504)	P value
Characteristics, n (%)						
Age, mean (SD)	74.4 (10.5)	74.3 (10.2)	73.4 (11.2)	74.8 (11.0)	74.8 (11.0)	<0.001
Female	16 494 (45.0)	11 186 (44.7)	517 (40.2)	2671 (45.6)	2120 (47.1)	<0.001
Townsend quintile, median (IQR)	2 (1–4)	2 (1–4)	2 (1–3)	3 (1–4)	3 (1–4)	
1	8862 (24.2)	6124 (24.5)	345 (26.9)	1347 (23.0)	1046 (23.2)	<0.001
2	8269 (22.6)	5706 (22.8)	321 (25.0)	1300 (22.2)	942 (20.9)	
3	7330 (20.0)	4964 (19.9)	270 (21.0)	1231 (21.0)	865 (19.2)	
4	5864 (16.0)	4065 (16.3)	185 (14.4)	897 (15.3)	717 (15.9)	
5	3800 (10.4)	2540 (10.2)	98 (7.6)	574 (9.8)	588 (13.1)	
Missing	2527 (6.9)	1609 (6.4)	66 (5.1)	506 (8.6)	346 (7.7)	
Comorbidities, n (%)						
Heart failure	2700 (7.4)	1908 (7.6)	79 (6.2)	387 (6.6)	326 (7.2)	0.016
Hypertension	22 955 (62.6)	15 824 (63.3)	751 (58.4)	3612 (61.7)	2768 (61.5)	<0.001
Diabetes mellitus	6691 (18.3)	4594 (18.4)	210 (16.3)	1058 (18.1)	829 (18.4)	0.31
Stroke/transient ischaemic attack	4622 (12.6)	3096 (12.4)	160 (12.5)	735 (12.6)	631 (14.0)	0.026
Vascular disease	4793 (13.1)	3316 (13.3)	149 (11.6)	717 (12.3)	611 (13.6)	0.052
Alcohol misuse	977 (2.7)	589 (2.4)	36 (2.8)	175 (3.0)	177 (3.9)	<0.001
Chronic kidney disease	7844 (21.4)	5426 (21.7)	221 (17.2)	1229 (21.0)	968 (21.5)	0.002
Liver disease	100 (0.3)	67 (0.3)	4 (0.3)	15 (0.3)	14 (0.3)	0.94
Hypercholesterolaemia	26 328 (71.8)	17 979 (71.9)	915 (71.2)	4172 (71.3)	3262 (72.4)	0.56
Smoking status						
Current smoker	3374 (9.2)	2272 (9.1)	103 (8.0)	585 (10.0)	414 (9.2)	<0.001
Ex-smoker	13 928 (38.0)	9711 (38.8)	484 (37.7)	2125 (36.3)	1608 (35.7)	
Never smoked	18 484 (50.4)	12 472 (49.9)	666 (51.8)	2993 (51.1)	2353 (52.2)	
Not indicated	866 (2.4)	553 (2.2)	32 (2.5)	152 (2.6)	129 (2.9)	
Risk scores, n (%)						
CHA_2DS_2-VASc						
0–1	5856 (16.0)	3887 (15.5)	263 (20.5)	984 (16.8)	722 (16.0)	<0.001
2	7192 (19.6)	4939 (19.8)	279 (21.7)	1106 (18.9)	868 (19.3)	
3–4	17 894 (48.8)	12 324 (49.3)	571 (44.4)	2850 (48.7)	2149 (47.7)	
5–9	5710 (15.6)	3858 (15.4)	172 (13.4)	915 (15.6)	765 (17.0)	
HASBLED-1						
0–2	28 279 (77.2)	19 298 (77.2)	1047 (81.5)	4508 (77.0)	3426 (76.1)	<0.001
3–8	8373 (22.8)	5710 (22.8)	238 (18.5)	1347 (23.0)	1078 (23.9)	
Drugs, n (%)						
Aspirin	20 510 (56.0)	14 175 (56.7)	683 (53.2)	3116 (53.2)	2536 (56.3)	<0.001
Statin	17 185 (46.9)	11 803 (47.2)	551 (42.9)	2651 (45.3)	2180 (48.4)	<0.001
Blood pressure-lowering drugs	29 136 (79.5)	20 007 (80.0)	961 (74.8)	4563 (77.9)	3605 (80.0)	<0.001
Number of drugs, mean (SD)	5.5 (2.2)	5.5 (2.2)	5.3 (2.2)	5.5 (2.2)	5.7 (2.2)	<0.001

CHA_2DS_2-VASc, Congestive heart failure; Hypertension, Age≥75 years; Diabetes mellitus; Stroke, Vascular disease; Age 65-74 years; Sex category ; HASBLED-1, Hypertension; Abnormal renal/liver function; Stroke; Bleeding; Labile INR; Elderly; Drugs or alcohol; VKA, vitamin K antagonist.

was highest for apixaban and lowest for VKA and dabigatran (figure 2).

In univariable analysis, apixaban had the lowest (HR 0.53, 0.50–0.57) and dabigatran had the highest (HR 1.02, 0.93–1.11) risk of non-persistence at 1 year, relative to VKA. Table 3 illustrates the optimal multivariable model, where the effects of CHA_2DS_2VASc and OAC required an interaction term with time since first OAC prescription. The interaction between time and date of first prescription shows that immediately following first prescription, apixaban still had the lowest risk (0.53, 0.46–0.60) and dabigatran the highest (1.24, 1.08–1.42), relative to VKA. The risk of non-persistence did not change over time for apixaban (0.91, 0.78–1.06 per year), but reduced over time for dabigatran (0.75, 0.65–0.86 per year) and rivaroxaban (0.69, 0.62–0.77 per year). Immediately after the first prescription, increasing comorbidity, when measured by CHA_2DS_2VASc score, was associated with reduced risk of non-persistence (0.71, 0.66–0.76; 0.66, 0.62–0.71; and 0.69, 0.63–0.76 for CHA_2DS_2VASc scores 2, 3–4 and 5–9, respectively, compared with CHA_2DS_2VASc scores 0–1). However, this risk was lessened over time (1.05, 0.99–1.12 and 1.13, 1.06–1.20 per year for CHA_2DS_2VASc scores 2 and 5–9, respectively). There was no significant effect of HASBLED-1 (1.04, 0.99–1.08 for HASBLED-1 scores ≥3, compared with HASBLED-1 scores 0–2), nor for the number of drugs or Townsend quintile (table 3). Overall, risk of non-persistence increased from 2011 until 2016 (1.03, 1.01–1.05 per year). Heart failure, vascular disease, chronic kidney disease, prior bleeding and alcohol misuse were associated with

Table 2 Likelihood of non-adherence by oral anticoagulant

	Univariable OR (95% CI)	Multivariable OR (95% CI)	
n	33 960	31 615	P value
VKA	1.00 (–)	1.00 (–)	
Dabigatran	0.53 (0.47 to 0.60)	0.54 (0.48 to 0.62)	<0.001
Rivaroxaban	0.61 (0.58 to 0.65)	0.76 (0.71 to 0.82)	
Apixaban	0.57 (0.54 to 0.61)	0.77 (0.71 to 0.84)	
CHA_2DS_2VASc			
0–1		1.00 (–)	
2		1.00 (0.93 to 1.08)	<0.001
3–4		0.94 (0.88 to 1.01)	
5–9		0.81 (0.74 to 0.89)	
HASBLED-1			
0–2		1.00 (–)	
3–9		0.98 (0.93 to 1.05)	0.62
Number of drugs			
Continuous/Linear		0.99 (0.98 to 1.00)	0.067
Townsend quintile			
1		1.00 (–)	
2		0.93 (0.87 to 0.99)	<0.001
3		0.86 (0.80 to 0.91)	
4		0.91 (0.85 to 0.97)	
5		0.86 (0.80 to 0.94)	
Date of first prescription* (years after 1 January 2011)			
Continuous/Linear		1.29 (1.22 to 1.37)	<0.001
Continuous/Quadratic		0.94 (0.93 to 0.95)	
BIC	46 263.63	42 880.41	

*Time difference (in years) between the date of the first ever OAC prescription for each patient and the start date of the study (1 January 2011). This suggests that the maximum effect of calendar time occurs at –ln(1.29)(2×/ln(0.94))=2.13 years.
BIC, Bayes information criterion; CHA2DS2-VASc, Congestive heart failure, Hypertension, Age≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category ; HASBLED-1, Hypertension; Abnormal renal/liver function; Stroke; Bleeding; Labile INR; Elderly; Drugs or alcohol; OAC, oral anticoagulant; VKA, vitamin K antagonist.

increased risk of non-persistence, while hypertension and age >65 years were associated with reduced risk. Non-persistence was more likely for dabigatran soon after initiation, but the effect relative to VKA and to apixaban declined over the period of an individual's prescription, although this did not happen relative to rivaroxaban (Online supplementary web tables 5a and 5b). Baseline characteristics are presented by 1-year persistence status in online supplementary web table 6.

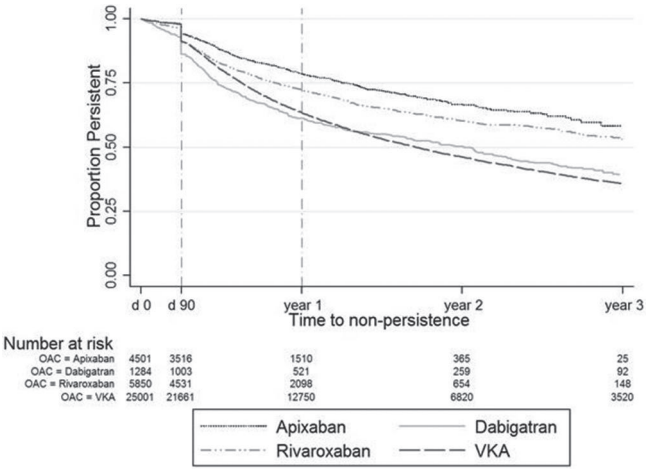

Figure 2 Kaplan-Meier analysis of persistence over time. OAC, oral anticoagulant; VKA, vitamin K antagonist.

Table 3 Risk of non-persistence by oral anticoagulant

	Univariable HR (95% CI)	Multivariable HR (95% CI)
n	36 636	34 109
OAC (effect on first prescribing)		
VKA	1.00 (–)	1.00 (–)
Dabigatran	1.02 (0.93 to 1.11)	1.24 (1.08 to 1.42)
Rivaroxaban	0.71 (0.67 to 0.74)	0.85 (0.77 to 0.93)
Apixaban	0.53 (0.50 to 0.57)	0.53 (0.46 to 0.60)
Time-dependent effect of OAC (per year of prescriptions)		
VKA		1.00 (–)
Dabigatran		0.75 (0.65 to 0.86)
Rivaroxaban		0.69 (0.62 to 0.77)
Apixaban		0.91 (0.78 to 1.06)
CHA_2DS_2VASc (effect on first prescribing)		
0–1		1.00 (–)
2		0.71 (0.66 to 0.76)
3–4		0.66 (0.62 to 0.71)
5–9		0.69 (0.63 to 0.76)
Time-dependent effect of CHA_2DS_2VASc (per year of prescriptions)		
0–1		1.00 (–)
2		1.05 (0.99 to 1.12)
3–4		1.12 (1.07 to 1.18)
5–9		1.13 (1.06 to 1.20)
HASBLED-1		
0–2		1.00 (–)
3–9		1.04 (0.99 to 1.08)
Number of drugs		1.00 (0.99 to 1.01)
Townsend quintile		
1		1.00 (–)
2		0.99 (0.95 to 1.03)
3		0.95 (0.91 to 1.00)
4		0.97 (0.93 to 1.02)
5		0.97 (0.92 to 1.03)
Date of first prescription* (years after 1 January 2011)		1.03 (1.02 to 1.05)

*Time difference (in years) between the date of the first ever OAC prescription for each patient and the start date of the study (1 January 2011) .
CHA2DS2-VASc, Congestive heart failure, Hypertension, Age≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category; HASBLED-1, Hypertension; Abnormal renal/liver function; Stroke; Bleeding; Labile INR; Elderly; Drugs or alcohol; OAC, oral anticoagulant; VKA, vitamin K antagonist.

Persistence and adherence

Of 36 652 individuals, 31.0% had <1 year of data, and of these 15.8% had primary non-adherence, 27.9% were non-adherent and 56.2% were adherent. Among 25 263 individuals with ≥1 year of data, primary non-adherence (3.5%) was less common than non-adherent, non-persistent (21.2%), adherent, non-persistent (8.6%), non-adherent, persistent (26.5%), and persistent, adherent (40.2%). Differences between OACs were significant (p<0.001). Primary non-adherence was highest with dabigatran (7.8%) and lowest (2.7%) with apixaban, while persistent adherence was highest with apixaban (50.7%) and lowest with VKA (38.2%). Non-adherent, non-persistence was greatest with VKA (23.4%) and least with apixaban (12.4%). Non-adherent persistence was highest with apixaban (29.0%) and lowest with dabigatran (19.5%) (table 4).

Table 4 Adherence and persistence by oral anticoagulant

	Overall	VKA	Dabigatran	Rivaroxaban	Apixaban
Total, n (%)	36 652	25 008	1285	5855	4504
Zero follow-up	16 (0.04)	7 (0.03)	1 (0.08)	5 (0.09)	3 (0.07)
Total <1 year of data	11 373 (31.0)	5307 (21.2)	441 (34.3)	3014 (51.5)	2611 (58.0)
Primary non-adherence	1800 (15.8)	818 (15.4)	78 (17)	531 (17.6)	373 (14.3)
Non-adherent	3178 (27.9)	1654 (31.2)	94 (21.3)	771 (25.6)	659 (25.2)
Adherent	6395 (56.2)	2835 (53.4)	269 (61.0)	1712 (56.8)	1579 (60.5)
Total ≥1 year of data	25 263 (68.9)	19 694 (78.8)	843 (65.6)	2836 (48.4)	1890 (42.0)
Primary non-adherence	876 (3.5)	631 (3.2)	66 (7.8)	128 (4.5)	51 (2.7)
Non-adherent, non-persistent	5352 (21.2)	4616 (23.4)	124 (14.7)	378 (13.3)	234 (12.4)
Adherent, non-persistent	2173 (8.6)	1711 (8.7)	132 (15.7)	232 (8.2)	98 (5.2)
Non-adherent, persistent	6699 (26.5)	5221 (26.5)	164 (19.5)	766 (27.0)	548 (29.0)
Persistent, adherent	10 163 (40.2)	7515 (38.2)	357 (42.3)	1332 (47.0)	959 (50.7)

VKA, vitamin K antagonist.

Switching

In non-persistent individuals, switching rates were 20.3%, 18.8%, 40.3%, 27.0% and 18.5% for all OACs, VKA, dabigatran, rivaroxaban and apixaban, respectively. In primary non-adherent individuals, the corresponding rates were 45.2%, 40.9%, 69.1%, 51.2% and 44.7%, respectively (online supplementary web table 7). When 'switching' was censored rather than 'non-persistent', differences between OACs were more consistent over time (since first prescription) and non-persistence was generally lower for dabigatran than VKA, with an increasing trend in the difference with time on OAC. The effect was less for other DOACs relative to VKA (online supplementary web figure 1 and web table 8).

DISCUSSION

In this study of long-term persistence and adherence across all OACs in AF, we have four findings. First, primary non-adherence is uncommon (3.5%), and over time on a DOAC the likelihood of non-adherence and non-persistence increases. Second, the proportion of individuals on OACs who are both adherent and persistent at 1 year is low (40.2%), with heterogeneity across different OACs. Third, population-level time trends in adherence and persistence exist after new drugs (DOACs in this case) are introduced. Fourth, increased comorbidities were associated with reduced risk of non-adherence and non-persistence for DOACs, but the number of drugs was not.

Observed rates of primary non-adherence for OAC are comparable with a recent Spanish study using large-scale regional EHR.[12] Primary non-adherence varies across different drugs, but our estimates appear lower than other chronic disease medications (≤20.8% for lipid-lowering drugs[23]). Rates are generally lower in European populations[23] than in North America, probably due to greater provision of prescription medication in public-funded health systems. Our results suggest that improved adherence and persistence requires longer-term monitoring, rather than current strategies emphasising drug adherence postinitiation. Greater switching with dabigatran than other OACs may reflect greater discontinuation (due to dyspepsia or other side effects[3]) or prescription patterns favouring other DOACs.[24]

For drugs to be effective, both adherence and persistence are prerequisites. It is therefore concerning that adherent persistence at 1 year after initial prescription ranged from only 38.2% to 50.7% for VKA and apixaban, respectively. Non-adherent, non-persistent individuals constituted 23.4% and 12.4% for users of VKA and apixaban, respectively (table 4). Adherence and persistence should be considered in combination, yet this is rare in both research and clinical practice.[25] Furthermore, observations that non-adherent, persistence is more common than adherent, non-persistence and that these proportions vary by type of OAC highlight the need for measurement of both metrics and potential for personalising approaches to improved drug utilisation. Factors which influence choice of drug in the same class include pharmacodynamics, pharmacokinetic, tolerability and cost,[26] to which adherence and persistence may be added.

DOACs are unusual for several new drugs in the same class entering the market in a short timeframe. Other examples are statins, antihypertensives and novel hypoglycaemic agents, but four new drugs in a 5-year period is extraordinary. DOACs have proven efficacy and effectiveness over VKA, and appropriate prescribing of OACs in AF has improved in the UK between 2000 and 2016.[27] However, there have been variations in prescription across DOACs over time.[28] Our analyses add that when DOACs were first prescribed, persistence to all DOACs appears to have been initially higher than to VKA and in some cases increase further over time on the OAC, with clear differences between different OACs. Findings were sensitive to how switching of drugs was considered, with persistence to dabigatran, which had the highest rates of 'switching', appearing much lower than VKA when 'switchers' were classed as 'non-persistent' versus censored ('no longer observed for that OAC'). Other possible reasons for differences between OACs include side effect profile, marketing strategies, and varying procurement and prescription practices. Adherence and persistence can have far-reaching implications on drug cost, effectiveness and policy at the population level[29] and should be monitored at the population level.

Our findings are consistent with previous studies which have shown associations between polypharmacy[12 30] and increased comorbidities[25] and reduced risk of non-adherence or non-persistence for OACs and other cardiovascular medications. Understanding each of the multiple steps in the prescription-persistence cascade may aid design and implementation of better interventions to improve drug utilisation. In routine clinical practice, EHR-based methods may be used to highlight individuals at greater risk of non-adherence or non-persistence, for example, by suggesting that persistence should be more of a focus for improvement than adherence, or for monitoring long-term adherence/persistence.

The major strength of our analysis is consideration of the relationship between adherence and persistence together across all DOACs and VKA in the same population. As well as socio-demographic, health and medication characteristics, the influence of time was also analysed. Even in large-scale data sets with

Key messages

What is already known on this subject?

- Despite proven efficacy for stroke prevention in atrial fibrillation, adherence and persistence are suboptimal for oral anticoagulants (OACs).
- Adherence and persistence are rarely studied together in the same population across all anticoagulants, taking into account all baseline factors in electronic health records.

What might this study add?

- This is the first study evaluating the time trends, predictive factors and associations between adherence and persistence of anticoagulants in atrial fibrillation in a population-based study in electronic health records.
- Persistence and adherence to OACs are relatively low at 1 year and there is heterogeneity across different OACs.
- There are significant variations over time that a patient is on a direct oral anticoagulant (DOAC), and population-level time trends in adherence and persistence after new drugs (DOACs in this case) are introduced.

How might this impact on clinical practice?

- Interventions should focus on improving adherence and persistence together and across drugs.
- These data may help to better understand the determinants of adherence and persistence, and to design and target interventions.

prescription data, there are several limitations. First, we did not have dispensing data, and therefore used previously validated methods to estimate adherence/persistence from prescription data. Our methods may be more uncertain for VKA than for DOACs (eg, differential impact of varying prescription gaps on persistence), possibly due to patients on warfarin often having longer duration prescriptions than DOACs. Second, missing prescription data meant that not all eligible individuals could be included due to incompleteness of follow-up. On the other hand, these are real-world data, which are routinely available and nationally representative. Third, relatively small numbers of patients could be included for DOACs, but numbers were comparable with other studies. Fourth, TTR would be a better measure of adherence for VKA but could not be estimated in our analysis due to lack of INR data (which also limited our HASBLED analysis). Finally, we focused on initial OAC prescription in OAC-naive patients to minimise bias in adherence/persistence based on previous OAC use, but did not focus on second and subsequent OACs used, where there would be more bias and greater consideration of overall treatment pattern which requires consideration of multidrug, multidisease adherence/persistence over time.

CONCLUSIONS

Our study shows changes in adherence and persistence for DOACs over time in AF. Since these are usually lifelong therapies, more emphasis should be placed on long-term adherence and persistence in clinical practice and research. Standardisation is required for EHR methods of adherence and persistence estimation across drugs, diseases and data sets. Persistence and adherence may have different determinants and should be studied together in EHR. Better understanding of these factors will lead to interventions which are more likely to improve adherence and persistence at individual and population levels across OACs and other drugs. Postmarketing surveillance should take into account adherence and persistence particularly for multiple drugs in the same class where head-to-head trials are unlikely.

Correction notice Since this article was first published online, open access has been selected.

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