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## ORIGINAL REPORT

# Use of direct oral anticoagulants in patients with atrial fibrillation in Scotland: Applying a coherent framework to drug utilisation studies

Tanja Mueller<sup>1</sup>  | Samantha Alvarez-Madrado<sup>1</sup>  | Chris Robertson<sup>2</sup> | Marion Bennie<sup>1,3</sup>

<sup>1</sup>Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK

<sup>2</sup>Department of Mathematics and Statistics, University of Strathclyde, Glasgow, UK

<sup>3</sup>Public Health and Intelligence Strategic Business Unit, NHS National Services Scotland, Edinburgh, UK

**Correspondence**

M. Bennie, Strathclyde Institute of Pharmacy and Biomedical Sciences, Robertson Trust Wing, University of Strathclyde, 40 Taylor Street, Glasgow, UK.

Email: marion.bennie@strath.ac.uk

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**Abstract**

**Purpose:** To report the use of direct oral anticoagulants (DOACs) for stroke prevention in patients with atrial fibrillation in Scotland and advocate the standardisation of drug utilisation research methods.

**Methods:** Retrospective cohort study using linked administrative data. Patients included those with a diagnosis of atrial fibrillation (confirmed in hospital) who received a first prescription for a DOAC (dabigatran, rivaroxaban, or apixaban) from September 2011 to June 2014. Drug utilisation measures included discontinuation, persistence, and adherence.

**Results:** A total of 5398 patients (mean CHA<sub>2</sub>DS<sub>2</sub>-VAsC score 2.98 [SD 1.71], 89.7% with ≥5 concomitant medicines) were treated with DOACs for a median of 228 days (interquartile range 105–425). Of 35.6% who discontinued DOAC treatment, 11.0% switched to warfarin, and 48.3% reinitiated DOACs. Persistence after 12 and 18 months was 75.9% and 69.8%, respectively. Differences between individual DOACs were observed: Discontinuation rates ranged from 20.4% (apixaban) to 60.6% (dabigatran) and 12 months persistence from 60.1% (dabigatran) to 85.5% (apixaban). Adherence to treatment with all DOACs was good: Overall DOAC median medication refill adherence was 102.9% (interquartile range 88.9%–115.5%), and 82.3% of patients had a medication refill adherence > 80%.

**Conclusions:** In Scotland, adherence to DOAC treatment was good, and switching from DOAC to warfarin was low. However, discontinuation and persistence rates were variable—although treatment interruptions were often temporary.

To decrease the inconsistencies in drug utilisation methods and facilitate meaningful study comparison, the use of a coherent framework—using a combination of discontinuation, persistence, and adherence—and the standardisation of measurements is advocated.

**KEYWORDS**

adherence, atrial fibrillation, discontinuation, DOAC, persistence, pharmacoepidemiology

Parts of an earlier version of the paper's content have been presented as a poster at the International Conference on Pharmacoepidemiology and Therapeutic Risk Management in Dublin, August 2016.

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## 1 | INTRODUCTION

Drug utilisation research (DUR) is frequently conducted to analyse the use of drugs, and a core aspect is adherence to drug treatment, defined as the extent to which patients take drugs according to prescribing

instructions.<sup>1</sup> Nonadherence to drugs is widespread<sup>1-3</sup> and has been linked to increases in morbidity, premature death, and health care expenditure;<sup>1,4,5</sup> especially nonadherence to drugs with complex pharmacological profiles such as warfarin and other vitamin K antagonists (VKAs) is known to negatively affect treatment outcomes.<sup>6-9</sup>

Warfarin is used for multiple cardiovascular conditions, and high discontinuation rates of warfarin treatment have been reported in clinical trials and observational studies;<sup>10-12</sup> poor adherence has been ascribed to a variety of issues, from the occurrence of bleeding events to the inconvenience of treatment.<sup>6,13-15</sup> As warfarin is widely used long-term in patients with atrial fibrillation (AF)—a common condition causing irregular heart-beat and, as such, a major independent risk factor for stroke<sup>16,17</sup>—efforts to replace warfarin have resulted in 4 new direct oral anticoagulants (DOACs) being introduced since 2008: dabigatran, a direct thrombin inhibitor, and rivaroxaban, apixaban, and edoxaban, direct factor Xa inhibitors.

Treatment with DOACs follows easier dosing schemes and theoretically requires no monitoring, primarily because their therapeutic windows are wider and interactions with other drugs/foods are shown to be less than with warfarin.<sup>18,19</sup> Treatment with DOACs is deemed as effective and safe as with warfarin;<sup>20-23</sup> the effect of nonadherence on bleeding risk and stroke incidence among AF patients has been addressed but as yet not intensely studied.<sup>24,25</sup> Recently, concerns have been raised about the potential impact of no monitoring and the presence of multimorbidity and polypharmacy on DOAC adherence.<sup>24,26-29</sup> Knowledge about patients' adherence to DOACs in real life is however still limited, and studies conducted thus far differ in scale, methodology, and focus.<sup>25,30-41</sup>

Results emerging from DUR studies are frequently used to compare uptake and use of drugs over time and between regions. Additionally, information on treatment adherence can be used to improve the accuracy of drug exposure estimates when investigating treatment outcomes in clinical practice—as compared to clinical trials results.<sup>42</sup> Nevertheless, although a comprehensive framework of drug adherence and a common terminology for measuring adherence have been proposed by the European Society for Patient Adherence, Compliance and Persistence,<sup>43</sup> DUR studies still make use of a variety of definitions and measurements, with methods of calculation also differing.<sup>44-46</sup> The objective of this study is therefore 2-fold: first, to report on the use of DOACs for stroke prevention in patients with AF identified in Scottish secondary care; and second, to advocate the standardisation of DUR by applying an evolving methods approach, based on a sound theoretical framework and well-documented measurements of adherence.

## 2 | METHODS

In Scotland (population approximating 5.3 million<sup>47</sup>), all residents are covered by the publicly funded National Health Service (NHS), with most clinical services including prescriptions provided free of charge at the point of care.<sup>48</sup>

Prescription details have been derived from the Prescribing Information System (PIS)—an NHS Scotland national database created primarily for reimbursement purposes.<sup>49</sup> The PIS holds data on the prescribed and dispensed items, patients, and prescribers, including a range of drug-specific information based on the British National Formulary.<sup>49,50</sup> Clinical data have been extracted from the Scottish Morbidity Records/Hospital inpatients dataset

### KEY POINTS

- Using Scottish national administrative data, we analysed the utilisation of the direct oral anticoagulants (DOACs) dabigatran, rivaroxaban, and apixaban in 5398 patients with atrial fibrillation between September 2011 and June 2014.
- Adherence to DOAC treatment was good, and switching from DOAC to warfarin was low. However, discontinuation and persistence rates were variable.
- Standardisation of drug utilisation studies using the ESPACOM framework, combining measurements of discontinuation, persistence, and adherence, is strongly advocated.

(SMR01), comprising diagnostic codes according to the International Classification of Diseases, 10th edition, and Office of Population Censuses and Surveys procedural codes, 4th revision.<sup>51-53</sup> PIS and SMR01 have been linked using the Community Health Index, a unique patient identifier issued to all residents registered with a general practitioner in Scotland.<sup>54</sup>

The study population comprises patients with a diagnosis of AF, confirmed in secondary care between January 1997 and June 2014, who received a DOAC between the date of a drug's approval for the indication of stroke prevention in patients with AF in Scotland (dabigatran: September 2011; rivaroxaban: January 2012; and apixaban: January 2013) and June 2014. For details about inclusion and exclusion criteria, see Appendix 1. A patient's index date for study inclusion was the date of first recorded prescription for any DOAC; their individual end date was either date of death or removal from a Scottish general practitioner register for other reasons, or the study end date (June 30, 2014), whichever occurred first. To assess baseline characteristics of patients, all available hospital records 5 years prior to the index date have been used. A time period of 6 months before the index date has been applied to define concomitant medication. Dispensed quantities and prescription dates have been used throughout the study.

Drug utilisation can be divided into 3 distinct parts: initiation, implementation, and discontinuation.<sup>43,55</sup> While initiation and discontinuation indicate the start and end of a therapy, the process of implementation illustrates whether medication was taken as prescribed. To give a valid representation of patients' drug taking behaviour and enable analysis of drug exposure, duration and intensity of treatment should be taken into account. Hence, this study includes measures of both discontinuation/persistence and adherence. Discontinuation has been calculated using the refill-gap method with censoring of patients after the first discontinuation event,<sup>56</sup> defined as a gap of more than 28 days without supply following the assumed end of a prescription, based on summary statistics of the data and comparable to previous studies.<sup>30,35</sup> In addition, a second discontinuation rate—allowing for reinitiation of treatment during the study period—has been introduced (cessation rate). In line with the literature, persistence at prespecified points in time (6, 12, and 18 months after treatment initiation) has been assessed using the anniversary method to account for intermediary

**TABLE 1** Utilisation measurements as used in this study, definitions, and calculation methods

Measurement	Definition	Calculation
Discontinuation rate <sup>56</sup>	Discontinuation rate (refill-gap method)	Patients discontinuing treatment (ie, supply gap exceeding 28 days)
	Cessation rate (allowing for treatment interruptions)	Patients ceasing treatment (ie, no further prescription for any DOAC during the study period)
Persistence rate <sup>56</sup>	Persistence after 6, 12, and 18 months (anniversary method)	Patients still on treatment 6, 12, and 18 months after initiation
Adherence <sup>45</sup>	Medication refill adherence (MRA)	Exposure to medication covering the time period of treatment
	Compliance rate (CR)	Exposure to medication covering the time period of treatment
	Continuous, single-interval measure of medication availability (CSA)	Exposure to medication covering the time period between individual dispensations
		(Patients discontinuing treatment / patients initiating treatment) * 100
		(Patients ceasing treatment / patients initiating treatment) * 100
		(Patients with drug supply covering the anniversary date / patients with sufficient follow-up time) * 100
		(Total days' supply / total days in study) * 100
		(Total days' supply—last refill) / days first up to, but not including last refill) * 100
		(Days' supply per dispensing / days in dispensing interval) * 100

**TABLE 2** Patients' baseline characteristics, overall and by first drug prescribed

	DOAC (n = 5398)	Dabigatran (n = 1016)	Rivaroxaban (n = 3292)	Apixaban (n = 1090)
Calendar year of first prescription (%)				
2011	51 (0.9)	51 (5.0)	0	0
2012	911 (16.9)	411 (40.5)	500 (15.2)	0
2013	2426 (44.9)	405 (39.9)	1624 (49.3)	397 (36.4)
2014	2010 (37.2)	149 (14.7)	1168 (35.5)	693 (63.6)
Female (%)	2472 (45.8)	400 (39.4)	1548 (47.0)	524 (48.1)
Mean age first prescription (SD)	74.4 (11.3)	71.6 (11.8)	75.3 (10.9)	74.3 (11.5)
Patient age category at time of first prescription (%)				
<50	169 (3.1)	44 (4.3)	80 (2.4)	45 (4.1)
50-64	763 (14.1)	212 (20.9)	407 (12.4)	144 (13.2)
65-74	1453 (26.9)	306 (30.1)	862 (26.2)	285 (26.1)
75-84	2007 (37.2)	310 (30.5)	1279 (38.9)	418 (38.3)
85+	1006 (18.6)	144 (14.2)	664 (20.2)	198 (18.2)
Co-morbidities as included in CHA <sub>2</sub> DS <sub>2</sub> -VASc score (%) <sup>a</sup>				
Congestive heart failure	1007 (18.7)	163 (16.0)	608 (18.5)	236 (21.7)
Hypertension	2067 (38.3)	379 (37.3)	1268 (38.5)	420 (38.5)
Diabetes mellitus	840 (15.6)	151 (14.9)	533 (16.2)	156 (14.3)
Prior stroke/TIA	839 (15.5)	144 (14.2)	520 (15.8)	175 (16.1)
Vascular disease	547 (10.1)	96 (9.4)	347 (10.5)	104 (9.5)
Mean CHA <sub>2</sub> DS <sub>2</sub> -VASc score (SD)	2.98 (1.71)	2.65 (1.74)	3.07 (1.70)	3.03 (1.65)
Prior VKA use yes (%)	2595 (48.1)	479 (47.1)	1644 (49.9)	472 (43.3)
Concomitant antiplatelet use (%) <sup>b</sup>	599 (11.1)	91 (9.0)	364 (11.1)	144 (13.2)
Concomitant aspirin use (%) <sup>c</sup>	1846 (34.2)	411 (40.5)	1039 (31.6)	396 (36.3)
Concomitant NSAID use (%) <sup>b</sup>	327 (6.1)	80 (7.9)	176 (5.3)	71 (6.5)
Concomitant use of contraindicated drugs (%) <sup>d</sup>	118 (2.2)	9 (0.9)	78 (2.4)	31 (2.8)
Concomitant use of drugs that should be avoided (%) <sup>e</sup>	268 (5.0)	53 (5.2)	147 (4.5)	68 (6.2)
Mean number different drugs prior to DOAC initiation (SD)	10.8 (5.5)	9.8 (5.2)	11.0 (5.5)	11.0 (5.5)

Abbreviations: DOAC, direct oral anticoagulant; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

<sup>a</sup>Based on hospital records only—ICD-10 codes included in the CHA<sub>2</sub>DS<sub>2</sub>-VASc score can be found in Appendix 2.

<sup>b</sup>Excluding aspirin.

<sup>c</sup>Includes only prescribed aspirin—potential underestimation of use as aspirin can be acquired over-the-counter in Scotland.

<sup>d</sup>Dabigatran: itraconazole, ketoconazole; rivaroxaban and apixaban: carbamazepine, itraconazole, ketoconazole, phenytoin, rifampicin.<sup>50</sup>

<sup>e</sup>Dabigatran: carbamazepine, clarithromycin, phenytoin; rivaroxaban and apixaban: clarithromycin.<sup>50</sup>

treatment interruptions.<sup>56</sup> As no “gold standard” to quantify adherence has been agreed upon, triangulation of measurements selected based on a literature review has been applied. See Table 1 for details. Drug utilisation measures are ratios and are summarised using medians and interquartile ranges (IQRs).

Kaplan-Meier survival analysis has been used to calculate median time to discontinuation; follow-up has been censored after 1 year for apixaban and after 2 years for dabigatran and rivaroxaban. Events have been coded as 1 = treatment discontinuation and 0 = still on treatment at end of follow-up. All data analyses have been conducted using the R software, version 3.3.1.<sup>57</sup>

Because of the nature of the study, ethical approval was not required; however, use of the data has been approved by the appropriate Privacy Advisory Committee. The data were hosted and managed by the NHS Scotland National Safe Haven.

### 3 | RESULTS

A total of 5398 patients were included in the study, 48.1% of whom used a VKA in the 6-month period preceding DOAC treatment. Overall median follow-up time was 228 days (IQR 105-425), ranging from 124.5 days (IQR 54-226.2) for apixaban to 467 days (IQR 237.8-719.2) for dabigatran. The median number of DOAC prescriptions issued to patients was 5 (IQR 2-9); 15.6% of patients received only one DOAC prescription.

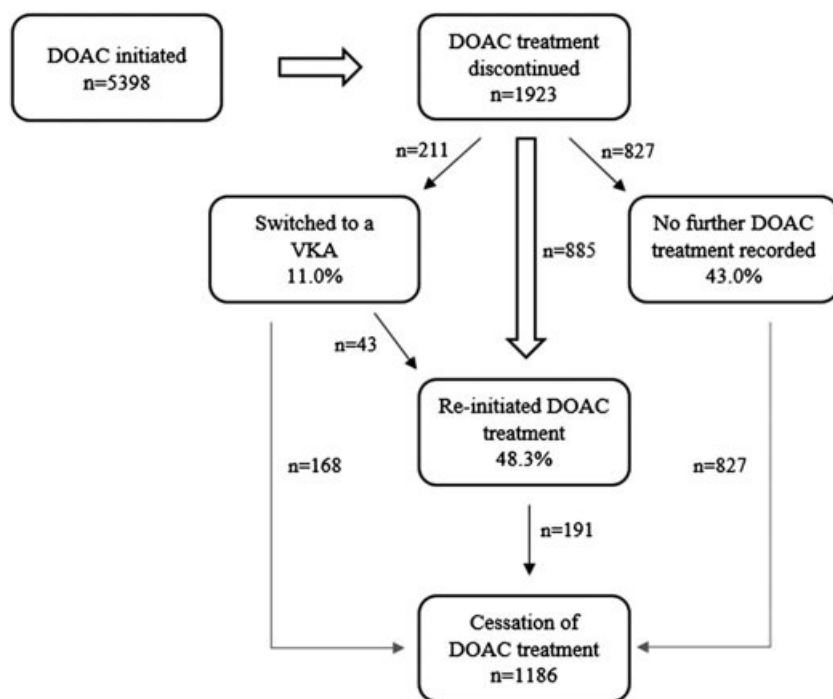
Multimorbidity and polypharmacy were widespread. Most patients (89.7%) were treated with 5 or more different drugs concomitantly; most prevalent medications were beta-blockers (66.5% of patients), statins (57.1%), drugs influencing the renin-angiotensin system (55.4%), diuretics (51.9%), and analgesics other than non-steroidal anti-inflammatory drugs (50.3%). Prior to treatment initiation, drugs that should either be avoided or are contraindicated in combination

with DOACs were prescribed to 5.0% and 2.2% of patients, respectively. Table 2 gives an overview of patients' baseline characteristics by first DOAC prescribed.

When looking at DOACs in general—ie, disregarding switches between individual drugs—1923 patients (35.6%) discontinued treatment during the study period, and the median time to discontinuation was 393 days (95% CI, 374-428 days); however, 48.3% of patients discontinuing reinitiated treatment with any DOAC at least temporarily (see Figure 1 for details). By study conclusion, 1186 patients had stopped receiving DOAC prescriptions, resulting in a cessation rate of 22.0%; this figure includes patients ceasing all oral anticoagulant treatment as well as those switching lastingly to a VKA.

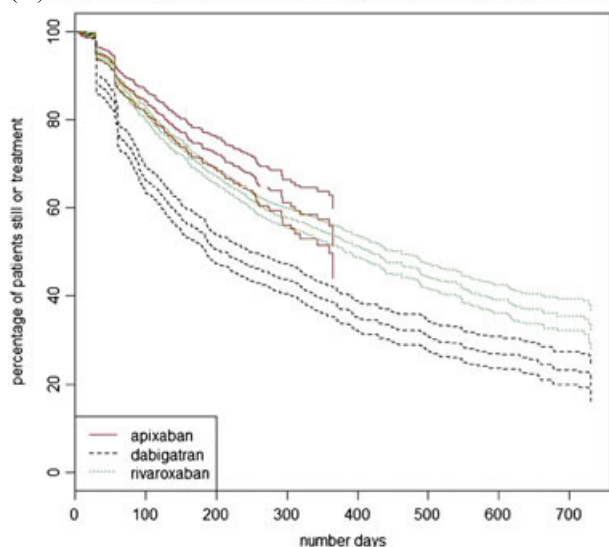
For individual DOACs, a total of 1995 patients (37.0%) discontinued treatment with the first drug prescribed, and discontinuation rates differed substantially between drugs: 20.4% apixaban, 35.1% rivaroxaban, and 60.6% dabigatran. Median time to discontinuation was considerably shorter for dabigatran (206 days; 95% CI, 185-247 days) than rivaroxaban (414 days; 95% CI, 382-462). While 35.1% of apixaban patients who discontinued restarted treatment, proportions for dabigatran and rivaroxaban were 44.2% and 46.1%, respectively; accounting for reinitiations, the share of patients who eventually ceased treatment with their index drug ranged from 14.4% for apixaban to 42.4% for dabigatran. Survival curves of patients discontinuing treatment, regardless of permanency, in contrast to patients ceasing treatment, are shown in Figure 2.

Crude persistence with DOAC treatment regardless of switches between individual drugs was 82.1%, 75.9%, and 69.8% at 6, 12 and 18 months, respectively. Persistence for individual drugs at 6, 12, and 18 months was 68.9%, 60.1%, and 54.7% for dabigatran and 83.5%, 79.0%, and 74.9% for rivaroxaban. Persistence with apixaban was 86.8% at 6 months and 85.5% at 12 months; insufficient data were available at 18 months.

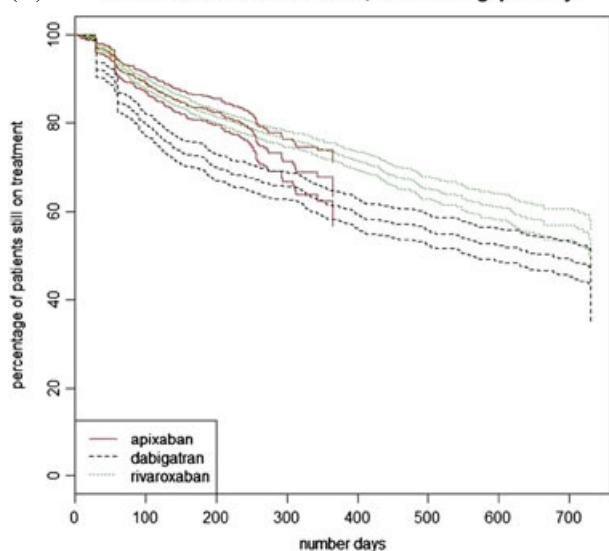


**FIGURE 1** Patients' treatment options after DOAC discontinuation. DOAC, direct oral anticoagulant; VKA, vitamin K antagonist

## (A) time to first discontinuation of treatment, admissible gap 28 days



## (B) time to cessation of treatment, admissible gap 28 days



Presented are Kaplan-Meier curves with 95% confidence intervals. Follow-up has been censored at 1 year for apixaban, and at 2 years for dabigatran and rivaroxaban; the vertical drop at the end of the lines is an artefact of this censoring. The drop at 1 month represents patients who received only one prescription during the study period.

**FIGURE 2** Kaplan-Meier survival curves by drug [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

Extending the length of admissible gap without drug supply from 28 to 56 days considerably decreased the DOAC discontinuation rate to 20.0%, but had less of an impact on persistence rates; persistence increased at 6 months to 85.8% and at 12 months to 77.9%. Relative differences between individual DOACs were not affected. Additional results of the sensitivity analysis can be found in Appendix 3.

A total of 4555 patients (84.4%) received at least 2 DOAC prescriptions and have been included in calculations of adherence to treatment. All adherence measurements gave comparable results and indicate high adherence to DOAC treatment, albeit with differences between individual drugs. Adherence remained stable over time when looking at 6 months intervals rather than assessing patients' entire treatment periods; see Table 3 for details.

## 4 | DISCUSSION

This is the first study in Scotland using linked data from PIS and SMR01 to analyse discontinuation, persistence, and adherence to DOAC treatment and one of a small number of studies analysing routinely collected data at a national level.<sup>25,33</sup> Additionally, it is one of the first studies to apply the European Society for Patient Adherence, Compliance and Persistence framework for drug utilisation studies<sup>43</sup> in combination with proposed standardised measurements for drug adherence;<sup>45</sup> it encompasses all dimensions of drug utilisation rather than focusing on a single aspect and therefore gives a much more comprehensive picture of how DOACs are used in clinical practice than previous studies.

Our findings are, at large, comparable to other research: AF patients being treated with DOACs are in general elderly, have high levels of co-morbidities, and receive a large number of additional drugs;<sup>31,32,34,38,58</sup> discontinuation of treatment varies considerably between individual DOACs;<sup>30,32,38,40</sup> and persistence declines over time.<sup>32,35</sup> Nevertheless, two important differences need to be highlighted: First, adherence to treatment was considerably higher in our study than has been reported in other studies conducted on a national level,<sup>25,33</sup> and second, switches from DOACs to VKAs were much less common than in previous observational studies.<sup>31,36,38</sup>

The crude discontinuation rate and 12 months persistence to DOAC treatment in Scotland were 35.6% and 75.9%, respectively, and similar rates have been reported before;<sup>35,41</sup> however, most studies reporting on discontinuation and/or persistence either did not explicitly describe how rates have been calculated or did not clearly distinguish between the different concepts of discontinuation and persistence. In our study, 48.3% of patients discontinuing treatment subsequently received at least one additional prescription for any DOAC, ie, eventually resumed treatment. When allowing for treatment interruptions by using only the number of patients where no subsequent DOAC prescriptions were recorded—a figure considerably influenced by length of follow-up, as more patients might reinitiate treatment over time—the crude DOAC discontinuation rate was 22.0%, highlighting that the method of calculation where patients are censored after the occurrence of a first discontinuation event likely leads to an over-estimation of discontinuation. This lower discontinuation rate is also more in agreement with the persistence rates found in this study, calculated using the anniversary method that is insensitive to periods of treatment interruptions.<sup>56</sup>

The percentage of patients switching from a DOAC to VKA treatment was low in this study (11.0%) compared to patients in Denmark (51.2%) and Japan (54%), but higher than in England (6.0%), and similar to the 1-year follow-up EORP-AF pilot registry (11.8%);<sup>35,36,38,59</sup> the reasons for these diverse findings are unclear, but might be rooted either in differences in clinical guidelines and physicians' preferences, or in timing of studies and availability of DOACs.

Although many studies report on DOACs as a group rather than separately by individual drugs, our results confirm previous findings indicating sizable differences between individual drugs: Dabigatran frequently exhibits discontinuation rates higher than rivaroxaban and apixaban.<sup>32,38</sup> Consequently, 12 months persistence has reportedly

**TABLE 3** Adherence to treatment, overall and by first drug prescribed

	DOAC (n = 4555)	Dabigatran (n = 864)	Rivaroxaban (n = 2821)	Apixaban (n = 822)
MRA > 80% (%) <sup>a</sup>	82.3	64.5	83.3	88.0
Median MRA (IQR) <sup>a</sup>	102.9 (88.9-115.5)	95.1 (56.7-107.1)	103.1 (90.3-115.0)	107.2 (93.5-124.7)
Median MRA over time (IQR) <sup>b</sup>				
0-6 months	108.9 (93.3-124.4)	100.0 (83.3-116.7)	108.9 (93.3-124.4)	111.7 (93.3-124.4)
7-12 months	112.0 (100.6-125.4)	110.6 (98.6-124.2)	111.5 (101.2-125.3)	111.7 (98.8-123.5)
13-18 months	112.0 (101.2-126.4)	112.0 (98.9-125.9)	112.0 (103.1-126.3)	n/a
CR > 80% (%) <sup>a</sup>	90.6	84.6	92.3	91.4
Median CR (IQR) <sup>a</sup>	103.5 (95.1-115.3)	100.6 (90.7-110.0)	103.7 (96.2-115.9)	104.7 (96.0-121.4)
Median CR over time (IQR) <sup>b</sup>				
0-6 months	105.3 (96.0-117.2)	103.5 (92.0-115.4)	105.7 (96.6-117.5)	104.2 (96.0-115.5)
7-12 months	100.0 (94.1-108.4)	100.7 (92.3-109.4)	100.0 (94.1-107.7)	100.0 (96.1-107.1)
13-18 months	100.8 (94.0-108.5)	101.4 (90.9-110.1)	100.6 (95.2-108.4)	n/a
Median CSA (IQR) <sup>a</sup>	100.0 (90.3-122.4)	100.0 (87.0-120.0)	100.0 (90.3-124.4)	103.4 (88.9-130.4)
Median CSA over time (IQR) <sup>b</sup>				
0-6 months	103.7 (90.3-133.3)	103.4 (88.2-130.4)	103.7 (90.3-133.3)	103.7 (90.3-133.3)
7-12 months	100.0 (90.3-116.7)	101.7 (88.2-120.0)	100.0 (90.3-116.7)	100.0 (88.7-112.0)
13-18 months	100.0 (90.3-116.7)	100.0 (88.2-117.6)	100.0 (90.3-116.7)	n/a

Abbreviations: CR, compliance rate; CSA, continuous, single-interval measure of medication availability; DOAC, direct oral anticoagulant; IQR, interquartile range; MRA, medication refill adherence.

To calculate adherence, only patients who received at least 2 prescriptions have been included. Discrepancies between the total number of patients receiving 2 prescriptions for any DOAC (n = 4555) and the sum of patients receiving at least 2 prescriptions for dabigatran, rivaroxaban, or apixaban (n = 4507) are due to patients switching drugs after only one prescription for an initial drug.

<sup>a</sup>Includes all patients with at least 2 prescriptions during the study period.

<sup>b</sup>Includes only patients with sufficient follow-up time to cover the respective prescription period.

been lowest for dabigatran, ranging from 44.7% to 74.4% compared to 60.1% to 77.4% for rivaroxaban and up to 85.9% for apixaban<sup>32,34</sup>—results that match our own findings of 60.1% (dabigatran), 79.0% (rivaroxaban), and 85.5% (apixaban).

Discontinuation of DOAC treatment has often been attributed to changes in underlying disease severity, including restoration of sinus rhythm, worsening kidney function, and side effects including bleeding events or, particularly in case of dabigatran, gastrointestinal disturbances.<sup>31,38,41</sup> Because of the data available for this study, specific reasons for treatment discontinuations among the study population remain unknown.

Adherence to medication was high for all drugs and did not considerably decline over time. Treatment gaps were rare, patients generally having enough medication to cover the treatment period; median medication refill adherence, and compliance rate during the first 6 months of treatment, indicated oversupply rather than undersupply of drugs, although these findings might be due to the timing of prescriptions. High median adherence to DOAC treatment has been shown before: between 94% and 99.7%<sup>37,39</sup> for dabigatran and up to 100% for rivaroxaban and apixaban.<sup>30</sup> Results differ however, which might in part be due to distinct methodology, as calculation methods for adherence and analysable time periods varied between studies. Moreover, results are frequently reported in dichotomised form, with a threshold of 80% of the calculated measurement used to identify adherent patients; findings using this approach range from 38.5% to 92.0% for dabigatran,<sup>25,33,34,37,39</sup> 50.5% to 96% for rivaroxaban,<sup>25,30,34</sup> and 61.9% to 95% for apixaban<sup>25,30,34</sup>—placing our findings of the proportion of patients with a compliance rate > 80% of 84.6%, 92.3%, and

91.4% for dabigatran, rivaroxaban, and apixaban, respectively, at the upper end of each scale. Comparing our findings obtained with 3 different adherence measurements, applied to the study data, illustrated how differences in calculation methods can impact the results; these observations raise concerns regarding comparability and generalisability of findings, especially when methods are not clearly described.

This study has a number of limitations. First, by identifying eligible patients to be included in the study in secondary care, patients diagnosed and treated exclusively in primary care were not captured. A recent study, conducted in England, identified that 42.1% of AF patients had an initial diagnosis in primary care;<sup>60</sup> however, as many of these patients are relatively elderly, a proportion might subsequently be admitted to hospital, and therefore, the percentage of patients potentially not included in our study is likely to be lower than 40%. We do not anticipate this having a large impact on our findings regarding adherence, persistence, and discontinuation. Second, the data used for analysis have not been collected for the specific purpose of this study but were gathered routinely in daily care. Therefore, not all desirable information was present; in particular, no indication for why drugs have been prescribed has been available. This might have resulted in the inclusion of patients who had AF but were treated with DOACs for other reasons—specifically, treatment with any DOAC for up to 6 months due to deep vein thrombosis—potentially leading to imprecision in results due to diverging anticipated treatment lengths and dosing schedules. In Figure 2, there is a small drop at 180 days of only about 3%, so the impact of this on persistence is likely to be small. Dose instructions as recorded by the prescriber have been used supplementary to drug supply based on standard dosing guidelines to

limit the impact of variations in dosing schedules on adherence. Finally, as prescription records do not cover secondary care, in-patient periods are not included; this might have impacted adherence and persistence, as hospital days could have appeared to be treatment interruptions. Sensitivity analysis of the lengths of admissible gaps and the additional measurement of treatment cessation have been used to account for the potential effect of in-patient episodes on discontinuation and persistence.

This study has nevertheless several strengths: Access to health care is universal, and electronic health records in Scotland cover the entire population. Because of the presence of a unique patient identifier, records can easily and reliably be linked; a large variety of variables is therefore available, including those essential for calculating adherence to medication. Furthermore, PIS and SMR01 have previously been used for research, and validity and accuracy of the data has been established.<sup>49,52</sup>

## 5 | CONCLUSION

In Scotland, adherence to DOAC treatment was high, and switching from DOAC to warfarin was low. However, discontinuation and persistence rates were variable—although treatment interruptions were often temporary. The effects of nonadherence, including treatment interruptions, on the safety and effectiveness of DOACs need to be investigated further; more research is needed to analyse whether treatment with DOACs does indeed result in better disease outcomes as compared to warfarin.

To decrease the inconsistencies in drug utilisation methodology impacting the comparability of results across studies, the use of a coherent framework—using a combination of discontinuation, persistence, and adherence—and the standardisation of measurements is strongly advocated.

## ETHICS STATEMENT

The authors state that no ethical approval was needed.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Appendix 1: Cohort identification and selection of study population

Appendix 2: ICD-10 codes as used for calculation of CHA<sub>2</sub>DS<sub>2</sub>-VASC scores at baseline

Appendix 3: Sensitivity analysis discontinuation and persistence

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