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Real-world persistence with direct oral anticoagulants (DOACs) in naïve patients with non-valvular atrial fibrillation☆

Eliana Ferroni [a,*], Nicola Gennaro [a], Giorgio Costa [b], Ugo Fedeli [a], Gentian Denas [c], Vittorio Pengo [c], Maria Chiara Corti [a]

[a] Epidemiological Department (SER), Azienda Zero, Padua, Italy
[b] Hospital Pharmacy, Provincial Authority for Health Services, Trento, Italy
[c] Cardiology Clinic, Department of Cardiac, Thoracic and Vascular Sciences, Padua University Hospital, Padua, Italy

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ABSTRACT

Background: Anticoagulation therapy is central for the management of stroke in patients with non-valvular atrial fibrillation (NVAF). Persistence with oral anticoagulation is essential to prevent thromboembolic complications.
Methods: We performed a population-based retrospective cohort study in the Veneto Region (north-eastern Italy, about 5 million inhabitants) using the regional health system databases. Naïve patients initiating direct oral anticoagulants (DOACs) for stroke prevention in NVAF from July 2013 to September 2017 were included in the study. Patients were identified using Anatomical Therapeutic Chemical (ATC) codes, excluding other indications for anticoagulation therapy using ICD-9CM codes. Treatment persistence was defined as the time from initiation to discontinuation of the therapy, including any therapeutic switching among DOACs. Baseline characteristics and comorbidities associated to the persistence of therapy with DOACs were explored by means of Kaplan-Meier curves and assessed through Cox regression.
Results: Naïve patients initiating direct oral anticoagulants for stroke prevention in NVAF identified in a 4.25-year period are 17,920. After one year, the persistence to the DOACs is 72.9%. Approximately 9.8% of the discontinuations are due to switch to vitamin k antagonists (VKAs). On multivariate analysis, factors negatively affecting persistence were female gender, age <65 years, renal disease and history of bleeding. On the other hand, persistence was better in patients with hypertension, previous cerebral ischemic events, and previous acute myocardial infarction.
Conclusion: In this study of real world data, one out four naive patients stopped treatment with DOACs within 12 months. Some characteristics may identify patients with poor persistence.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia diagnosed in clinical practice, and its prevalence is almost doubled in the last decade [1]. Patients with AF are at increased risk of thromboembolic events, heart failure, hospitalization, and death [2].

AF increases stroke risk fivefold across all ages [3]. Oral anticoagulants (OACs) substantially reduce this risk, and evidence-based guidelines recommend them in patients with one or more risk factors for stroke [4,5].

Among OACs, warfarin, an oral vitamin K agonist (VKA), has been the standard of care for more than half a century. However, VKAs are associated with several limitations including a narrow therapeutic window, need for blood monitoring with consequent dose adjustment, multiple interactions with drugs, supplements and food [6]. These limitations have a negative impact on the level of persistence to VKA therapy [7] and indirectly on the clinical benefits of therapy which are achieved if medication adherence remains high and patients are persistent.

Direct acting oral anticoagulants (DOACs) have revolutionized the management of anticoagulant therapy. Compared to VKA, they do not require blood monitoring and are characterized by a better safety profile [8]. In phase III trials including patients with non-valvular AF (NVAF), discontinuation rates differed between DOACs and warfarin, with some studies reporting more persistence with DOACs and others with VKAs [9,10]. Real-life cohort data on DOACs discontinuation in patients with non-valvular AF have been conflicting [11–13].

This population-based retrospective cohort study aims to measure persistence levels of DOACs, investigating also some possible predictors of treatment discontinuity in NVAF patients.

☆ Authors statement: All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: Epidemiological Department (SER), Azienda Zero of the Veneto Region, Passaggio Gaudenzio, 1 35131 Padua, Italy.
E-mail address: eliana.ferroni@azero.veneto.it (E. Ferroni).

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2. Methods

2.1. Study setting

We adopted a new-user retrospective cohort design to analyse persistence in patients initiating treatment with DOACs. To this purpose, we performed a population-based analysis on linked claims data in the Veneto Region using healthcare databases covering all individuals: the drug prescriptions archive, the regional inpatients register, the database of residents registered in the regional health system, the archive of co-payment exemptions. Specifically, the drug prescription database includes all prescriptions reimbursed by the National Health System, with information on purchase date, Anatomical Therapeutic Chemical (ATC) classification, and dosage and number of pills per package. The regional inpatients register includes all hospital admissions and discharge dates (both from private and public hospitals, of residents hospitalized both in regional facilities and outside the study area), and discharge diagnoses coded according to the International Classification of Disease, 9th Revision, Clinical Modification (ICD9-CM). The database of residents includes information on vital and emigration status. The archive of co-payment exemptions due to chronic diseases includes information on comorbidities. All analyses were carried out on routinely collected health records submitted to an anonymization process allowing linkage of archives without any possibility of identification of individuals. There was no patient involvement in this study.

2.2. Identification of patients with NVAF

We identified subjects aged 18 years or older by their index prescription of DOACs (dabigatran ATC: B01AE07, rivaroxaban ATC: B01AF01, apixaban ATC: B01AF02) from July 2013, date of the first DOAC commercialization approval in Italy, to September 2017. The first prescription, or index date, identified the date of enrolment in the cohort. We excluded from enrolment individuals with any dispensed prescription of any oral anticoagulant in the 12 months preceding the index date. Patients with dispensed prescriptions of antiplatelet drugs post-index date were also excluded from the study, since our cohort was originally created to study effectiveness and safety of OACs [14], and concurrent treatment with antiplatelet drugs would have influenced study outcomes. Linkage with the regional inpatients register allowed the exclusion of patients with mechanical heart valves, diagnosed mitral stenosis, venous thromboembolism or other indications for anticoagulation. Detailed description of the codes used to select NVAF patients were reported in a previous paper. [14]

2.3. Patient exposure

Patients were considered as being continuously exposed from the index date until the absence of a new prescription after a 60 day period following the calculated coverage of the last prescription fill (grace time).

A 60-day period was shown to be a clinically relevant length of time to obtain a new prescription and it was applied to assess DOACs persistence in other observational studies [15–17].

Switching among DOACs was not considered an event of discontinuity. Patients who died during the follow-up were censored. We measured drug exposure in terms of recommended dose by summary of product characteristics. The recommended dose of rivaroxaban for the treatment of NVAF is 15 or 20 mg once daily, dabigatran (110 or 150 mg) and apixaban (2,5 or 5 mg) are administered twice daily. The number of doses was converted to the number of days the patient was treated, counting one or two doses per day (once- or twice-daily dosage regimen, according to the DOAC) per day and distributing all available doses to days of follow-up (including the days covered by the last prescription). The last date of enrolment was 30 September 2017, while follow up extended until 31 December 2017 to allow a follow up of at least 3 months for all individuals. A sensitivity analysis was carried out restricted to patients enrolled by 31 December 2016, allowing for at least 365 days of follow-up.

2.4. Baseline demographics and clinical features of patients

Demographics and comorbidities were recorded at the time of enrolment in the cohort. By linkage of drug prescriptions, inpatients records, and co-payment exemptions, we identified patient comorbidities (through diagnoses coded in the previous 5 years) and use of drugs of interest (Clopidogrel, ASA, NSAIDs, Statins).

2.5. Statistical analysis

Kaplan-Meier estimates of survival were used to assess the persistence rate during the time of follow up (persistence curves). Persistence rates were calculated at 12 months of follow-up. We assessed the predictors for persistence to DOACs; multivariate Cox proportional hazard models were used to assess factors significantly associated with persistence. Variables considered were age at the index date, gender, hypertension, cancer, diabetes, stroke/TIA/thromboembolism, history of bleeding, myocardial infarction, renal disease, heart failure. All variables were tested to assure the requirement for proportionality; variables not satisfying the proportionality assumption were included as stratification factors in the Cox model.

Table 1
Characteristics of naive patients with NVAF (n. 17,920).

	Patients
Principal characteristics	N (%)
Gender	
Male	8638 (48.2)
Female	9282 (51.8)
Age groups	
0–64 yrs	2723 (15.2)
65–74 yrs	4297 (24.0)
75–84 yrs	6927 (38.7)
≥85 yrs	3973 (22.2)
Type of DOACs at index date	
Dabigatran	4167 (23.3)
Rivaroxaban	7750 (43.2)
Apixaban	6003 (33.5)
CHADS-VASc score	
<2	2421 (13.5)
2–3	6966 (38.9)
4–5	6524 (36.4)
>5	2009 (11.2)
Comorbidities	
Congestive heart failure/Left ventricular dysfunction	1640 (9.2)
Cancer	1698 (9.5)
Diabetes	2960 (16.5)
Hypertension	12,901 (72.0)
Stroke/TIA/thromboembolism	3617 (20.2)
Bleeding (10 years)	568 (3.2)
Renal disease	430 (2.4)
Myocardial infarction	451 (2.5)
Other concomitant therapies[a]	
ASA	5248 (29.3)
Clopidogrel	907 (5.1)
Nonsteroidal anti-inflammatory drugs	2647 (14.8)
Statins	6607 (36.9)

[a] >2 drug packages in the 12 months before the index date.

3. Results

Overall, 17,920 patients starting DOACs were identified in the period July 2013 to September 2017. Baseline characteristics are detailed in Table 1. Most patients were older than 74 years old, while gender was almost equally represented. Comorbidities included hypertension (72%), diabetes mellitus (17%), congestive heart failure (9%), previous stroke/TIA (20%), and prior myocardial infarction (2%). Moreover, almost 30% of the patients also had received aspirin and statins (>2 drug packages in the 12 months before the index date).

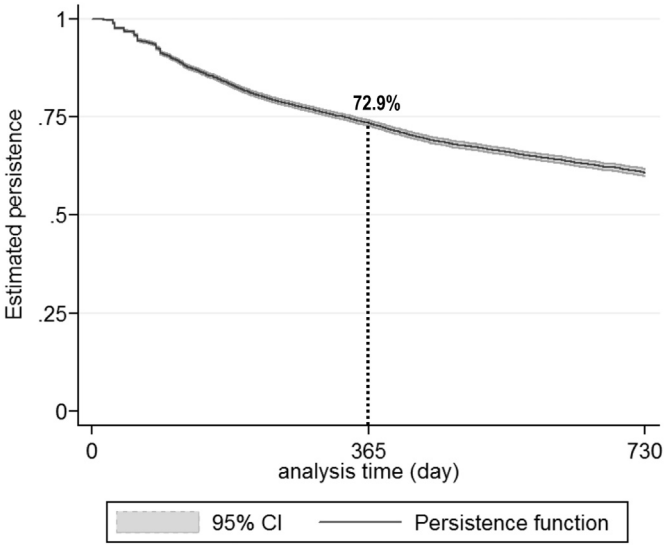

Fig. 1. Persistence rate for DOACs.

After one year, 27.1% of patients were not persistent to DOACs (Fig. 1); among these, 9.8% switched to vitamin k antagonists (VKAs). Restricting analysis to patients with at least 365 days of follow-up, persistence rate did not change substantially.

Looking at the Kaplan-Meier curves (Table 2), the main characteristics linked to poor persistence were age <65 years and low CHADSVASc score.

Factors affecting persistence on the multivariate Cox model are shown in Table 3, where an HR > 1 denotes a worse persistence and HR < 1 denotes better persistence. Younger age (HR 2.12; 95%CI 1.99–2.26), female gender (HR 1.10; 95%CI 1.04–1.16), renal disease (HR 1.39; 95%CI 1.31–1.80) and previous episodes of bleeding (HR 1.29; 95%CI 1.12–1.50) have a worse persistence. Conversely, patients with hypertension (HR 0.65; 95%CI 0.67–0.75), history of stroke or thromboembolic events (HR 0.76; 95%CI 0.71–0.82) or previous acute myocardial infarction (HR 0.76; 95%CI 0.62–0.93) are more persistent.

Table 3
Predictors of discontinuation for DOACs.[a]

Characteristics	HR	HR (95% CI)
Demographics		
Gender (Female vs male)	1.10	(1.04–1.16)
Age (≤65 yrs vs >65 yrs)	2.12	(1.99–2.26)
Other diseases		
Hypertension	0.65	(0.62–0.69)
Cancer	1.05	(0.96–1.15)
Diabetes	1.01	(0.93–1.08)
Renal disease	1.53	(1.31–1.80)
Stroke/TIA/thromboembolism	0.76	(0.71–0.82)
Acute myocardial infarction	0.76	(0.62–0.93)
Bleeding	1.29	(1.12–1.50)

[a] Stratified for chronic heart failure.

4. Discussion

In patients with NVAF on DOACs, we found an overall discontinuation rate at one year of 27.1%. Discontinuation rates from 15.4% to 32.2% during the first year of treatment were reported in small samples of NVAF patients treated with DOACs [18,19]. To our knowledge, this is the first Italian study reporting real-world evidence on DOACs persistence in a large sample of patients with NVAF, analysing also pattern of persistence in depth.

Our regression model identified a number of factors associated with poor treatment persistence. Younger age is negatively associated with persistence. Age <65 years was also found as an independent risk factor of anticoagulant discontinuation in a previous large-scale cohort study [20]. Other studies reported younger age affecting non-compliance to medications [21–23]. Younger patients may forget to take their medication because of their busier lifestyles and other priorities, despite understanding the role of treatment.

In our study female gender worsened medication persistence. The role of gender in affecting persistence is controversial. Several studies have found women to be more non-adherent than men [24,25], others suggested the opposite [26], while some other studies found no relationships between gender and adherence [27,28].

Patients with abnormal renal function were also less persistent. These patients have an increased risk for bleeding and thromboembolic complications. Since anticoagulants can promote bleeding episodes, and clear evidence-based recommendations in severe stages (eGFR <30 mL/min) cannot be given, treatment discontinuation may be not considered inappropriate.

History of bleeding was also related to poor persistence. Patients experiencing a previous bleeding episode may discontinue by themselves or in accordance with their general practitioner/specialist. Other studies reported bleeding side effects of DOACs as a common reason for non-persistence [11,29].

Conversely, patients with history of stroke, thromboembolism, or acute myocardial infarction were more likely to persist. This may be related to increased understanding in these patients of the importance of persistence with prescribed regimens. Persistence also improved in patients affected by hypertension.

Medication adherence represents a complex and dynamic behaviour. Many studies report that about 50% of patients do not take their long-term therapy for chronic conditions as prescribed [30,31]. This behaviour may be linked to many aspects, such as socio-economic status, as well as patient-related factors [30,32,33].

Real-world data is a key strength of our study, capturing a large number of patients with NVAF and removing the influence of experimental environment on patient persistence. Although analysis of claims data provides a good indication of real-world persistence of DOAC therapy as compared with more controlled environments, such as clinical trials, it also carries significant limitations. DOACs may be discontinued for a wide variety of interventions that may not have been fully captured and examined in our data, such as surgeries and procedures [34]. Drug persistence may be underestimated due to patients undergoing electricalcardioversion and, thus, being discontinued. In our cohort only few patients experienced this procedure (6.03%), and excluding

Table 2
Level of persistence by baseline characteristics of the cohort.

		Kaplan Meier
Characteristics	N	1 year (95% CI)
Total	17,920	72.9 (72.2–73.7)
Gender		
Male	8638	72.3 (71.2–73.3)
Female	9282	73.5 (72.5–74.5)
Age groups		
0–64 yrs	2723	50.4 (48.3–52.5)
65–74 yrs	4297	76.8 (75.4–78.2)
75–84 yrs	6927	78.0 (76.9–79.1)
≥85 yrs	3973	75.1 (73.9–76.9)
CHADS-VASc score		
<2	2421	47.4 (45.1–49.1)
2–3	6966	75.2 (74.2–76.5)
4–5	6524	78.4 (77.4–79.5)
>5	2009	78.1 (75.1–80.5)
CHF/Left ventricular dysfunction		
Yes	1640	72.8 (72.0–73.5)
No	16,280	72.8 (72.0–73.5)
Cancer		
Yes	1698	73.7 (71.2–76.1)
No	16,222	72.8 (72.0–73.5)
Diabetes		
Yes	2960	75.5 (73.7–77.2)
No	14,960	72.4 (71.6–73.2)
Hypertension		
Yes	12,901	77.6 (76.7–78.4)
No	5019	61.3 (59.8–62.7)
Stroke/TIA/thromboembolism		
Yes	3617	80.2 (79.4–82.3)
No	14,303	70.9 (70.1–71.7)
Bleeding		
Yes	568	73.1 (68–7 - 76.9)
No	17,352	72.9 (72.2–73.7)
Myocardial infarction		
Yes	451	80.5 (75.8–84.4)
No	17,469	72.8 (72.1–73.5)
ASA[a]		
Yes	5248	83.6 (82.5–84.7)
No	12,672	68.5 (67.5–69.3)
Clopidogrel[a]		
Yes	907	84.3 (81.4–86.7)
No	17,013	72.3 (71.5–73.1)
NSAIDs		
Yes	2647	74.7 (72.8–76.5)
No	15,273	72.6 (71.8–73.4)
Statins		
Yes	6607	79.8 (78.7–80.8)
No	11,313	68.9 (67.9–69.9)

[a] Treatments were measured at baseline. Patients using antiplatelet drugs during follow-up were excluded.

them from the analysis did not change our results. Hospitalizations could have influenced drug persistence. We analysed the period from the last prescription date, including grace time, and only 16.7% of discontinued patients were hospitalized over this period. Other important clinical information, such as disease severity and reasons of discontinuation, were not available. Moreover, the presence of important differences in patient characteristics (i.e. age, comorbidities, polypharmacy) did not allow us to perform persistence analysis for each DOAC.

Clinicians may have decided to change type of anticoagulant, i.e. switching to VKA, due to adverse effects occurred, leaving patients still in anticoagulant therapy. In our study switching to VKA occurred in 9.8% of patients not persistent to DOAC, and almost 20% of these patients switched again to DOAC after a short period of time.

5. Conclusions

Our results show that around one out of four naive patients with NVAF stop treatment with DOACs within 12 months. Some characteristics have a significant impact on poor persistence: gender, age, history of stroke/TIA/thromboembolism, previous bleeding, hypertension, renal disease. Efforts should be made in improving patients' persistence, through patient education and physician understanding of factors negatively influencing persistence.

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Conflicts of interest

Authors declare they do not have any conflicts of interest.

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