

Non-persistence risk and health care resource utilization of Italian patients with non-valvular atrial fibrillation

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Summary. The aim of this study is to compare discontinuation risk and health care resource utilization between the vitamin K antagonists (VKAs) and the non-vitamin K antagonist oral anticoagulants (NOACs) in newly treated patients with non-valvular atrial fibrillation (NVAf). Based on administrative databases of five Italian Local Healthcare Units, all patients with a discharge diagnosis of NVAf between 2011 and 2014 were selected. Among them, the incident users of NOACs and VKAs in 2014 were followed-up to from the first prescription date to the occurrence of anyone of the following events: a 90-days gap in therapy, switch to a different molecule or add-on of a different molecule into the regimen, death of patient, end of follow-up (December 2015). All-causes hospitalizations, outpatient visits and examinations within the persistence period were also evaluated. The final cohort was composed of 2909 and 765 incident users of VKA and NOACs, respectively. Cox regression to model time to non-persistence within 12 months showed a 62% reduction in risk of drug discontinuation in NOAC patients compared to VKA patients (HR, 0.38 [0.33-0.44]). In the adjusted analyses with warfarin as reference, apixaban patients (HR, 0.35 [0.24-0.50]) had the lowest risk of nonpersistence, followed by rivaroxaban (HR, 0.42 [0.33-0.54]) and dabigatran users (HR, 0.51 [0.43-0.61]). The mean total numbers of all-cause hospitalizations records in 12-months persistent patients were significantly less in NOACs users compared with VKA users (0.36 vs 0.47, p-value: 0.03). Similarly, the differences in the mean numbers of all-cause visits and examinations were statistically significant between VKA and NOAC patients, who registered on average 2.33 vs 1.84 visits (p-value: 0.01) and 24.4 vs 9.2 exams referrals (p-value: <.0001), respectively. NOACs showed a better profile in terms of both resource utilization and persistence compared with VKAs. In particular, apixaban returned the lowest risk of discontinuation than dabigatran and rivaroxaban.

Key words. Atrial fibrillation, Italy, NOAC, NVAf, VKA, persistence, resource utilization.

Rischio di non persistenza e utilizzo delle risorse sanitarie in pazienti italiani con fibrillazione atriale non valvolare.

Riassunto. Il presente studio intende confrontare il rischio di non persistenza e l'utilizzo delle risorse sanitarie nei pazienti con fibrillazione atriale non valvolare (FANV) naïve al trattamento con antagonisti della vitamina K (AVK) o con nuovi anticoagulanti orali (NAO). Partendo dai database amministrativi di cinque ASL italiane, sono stati selezionati e inclusi nello studio tutti i pazienti con almeno una dimissione ospedaliera per FANV dal 2011 al 2014. Tra questi, i nuovi utilizzatori di AVK o NAO nel 2014 sono stati identificati e seguiti a partire dalla data della prima prescrizione al verificarsi di uno qualsiasi dei seguenti eventi: interruzione della terapia superiore a 90 giorni, passaggio o aggiunta di una molecola differente rispetto a quella prescritta alla data indice, morte del paziente, fine del follow-up (dicembre 2015). I due gruppi sono stati, infine, confrontati per il numero medio di ospedalizzazioni per tutte le cause, di visite specialistiche e di esami effettuati nel periodo di persistenza alla terapia. La coorte finale era composta da 2909 nuovi pazienti trattati con AVK e 765 nuovi pazienti trattati con NAO. I risultati del modello di regressione di Cox hanno evidenziato una riduzione del rischio di non persistenza pari al 62% per i pazienti NAO rispetto ai pazienti AVK (HR, 0,38 [0,33-0,44]). Nel modello di confronto tra molecole con warfarin come gruppo di riferimento, i pazienti apixaban hanno mostrato il minor rischio di non persistenza (HR, 0,35 [0,24-0,50]), seguiti dai pazienti trattati con rivaroxaban (HR, 0,42 [0,33-0,54]) e dabigatran (HR, 0,51 [0,43-0,61]). In media, il numero di ospedalizzazioni per tutte le cause rilevato nei pazienti persistenti a 12 mesi si è mostrato significativamente inferiore tra i pazienti NAO rispetto ai pazienti AVK (0,36 vs 0,47, p-value: 0,03). Similmente, le differenze riscontrate nel numero medio di visite ed esami specialistici sono risultate statisticamente significative tra i pazienti AVK e NAO, i quali hanno registrato in media 2,33 vs 1,84 visite e 24,4 vs 9,2 esami (p-value: <.0001), rispettivamente. I pazienti NAO hanno mostrato sia un minore rischio di interruzione del trattamento, sia un minore consumo di risorse rispetto ai pazienti AVK. Infine, tra i NAO in analisi, apixaban ha mostrato il minore rischio di discontinuità alla terapia.

Parole chiave. AVK, FANV, fibrillazione atriale, Italia, NAO, persistenza, utilizzo delle risorse.

Introduction

Atrial fibrillation (AF) is a heart rhythm disorder characterized by an irregular heartbeat (arrhythmia) and represents one of the major causes of stroke, heart failure, blood clots and cardiovascular-related morbidity worldwide¹. The term 'non-valvular' describes cases where rhythm disturbance is not associated with mitral stenosis that has been the leading cause of AF and mechanical prosthetic heart valves in the past². AF prevalence stands at around 3% of adults aged ≥ 20 years, with higher prevalence rates in males (ratio of 1.2:1) and older people (10%-17% of those aged 80 years or older)³. This percentage is expected to rise in the coming years owing to the augmented detection of silent AF as well as the population's increased longevity⁴⁻⁶. People suffering from AF are associated with an increased risk of all-cause mortality and morbidity, such as heart failure and stroke⁷⁻⁹. In addition, the reduced exercise capacity and the left ventricular dysfunction entail a deterioration in the quality of life which, alongside with cognitive impairment and depressed mood, are associated to subsequent high rates of hospitalizations and 1.5 fold higher health care resource utilization and AF-related costs¹⁰⁻¹⁸. The milestones of AF management include anticoagulation and rhythm and rate control, even if the latter has been found to improve AF-related symptoms, but without reducing long-term morbidity or mortality^{19,20}. The oral anticoagulant therapy (OAT) with vitamin K antagonists (VKAs) or novel oral anticoagulants (NOACs) are crucial in reducing stroke and mortality in AF patients, particularly in those with pre-existing stroke risk factors, e.g. CHA₂DS₂-VASc score of 1 or more for men, and 2 or more for women^{21,22}. For as many as 50 years, warfarin has been the most widely used oral anticoagulant and, for patients who are not suitable for or choose not to take an anticoagulant, an antiplatelet therapy was recommended^{23,24}. Moreover, 2016 ESC guidelines on NVAF recommends the use on NOACs in preference to VKAs when OAC is initiated because of their greater ease of use, fewer drug-drug and drug-food interactions and a better safety and efficacy profiles without need for regular anticoagulation monitoring and dose adjustments¹. More recently, other studies have also shown significantly higher non-persistence rates and healthcare resource utilization (i.e., hospitalizations, emergency room visits and physician office visits) with VKA-treated users compared with NOACs²⁵⁻²⁸, but very little is known about the Italian experience about these issues²⁹. Therefore, the aim of the present study was to investigate the oral anticoagulants (OACs) usage and understand the AF management in the Italian real world setting using large administrative databases. For this purpose, an observational real-world study was designed to compare the non-persistence risk at 1 year between the VKAs and the NOACs users, as well as among the users of four molecules of interest (i.e., warfarin, apixaban, rivaroxaban, dabig-

atran) in newly treated patients with non-valvular AF (NVAF). Furthermore, demographic characterization and healthcare resource utilization associated with OACs were also investigated.

Methods

DATA SOURCE

This retrospective study was based on administrative databases of five Local Healthcare Units (LHUs) distributed over the Italian territory (Bergamo and Bus-solengo - Northern, Piacenza and Roma - Central, Palermo - Southern). The involved LHUs account for over 3.5 million registered inhabitants out of the 59.7 million inhabitants registered in Italy (2014 census). A unique identifier linked the different databases of each LHU that provided information on hospital discharge records, flow of drugs from pharmacies in the area, outpatient database, patients' demographics and death registry. Diagnoses and procedures associated with hospital utilization were recorded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), while prescription forms registered information on strength, number of tablets, and date of dispensation according to the Anatomical Therapeutic Classification codes (ATC).

The start of the project followed the approval by the pertinent Ethical Committees and Competent Authorities, in accordance with all the regulations in force and regulatory requirements.

STUDY POPULATION

All patients with at least one hospitalization related to a primary or secondary NVAF diagnosis (ICD9 code 427.31) between 1st January 2009 and 31st December 2014 were selected. Exclusion criteria was the presence of at least one hospitalization with a discharge diagnosis of heart valve surgery (DRG 104-105) and/or mitral and/or aortic valves disease (ICD9 code 394, 396). The final cohort consisted of patients who started treatment with an OAC or antiplatelet during 2014 and the date of the first prescription during this period constituted the entry date in the cohort (index date). The study was performed on treatment-naïve users, who were defined as patients without prescriptions of the same molecule in the year preceding the index date.

EXPOSURE DEFINITION AND OUTCOMES

Once retrieved the incident OAC and antiplatelet users, three groups were defined according to the first treatment class initiated in the study period: VKA (warfarin, acenocoumarol), NOAC (apixaban, dabigatran, rivaroxaban) and antiplatelet class (acetyl-

salicylic acid, ticlopidine, dipyridamole, clopidogrel, prasugrel, ticagrelor). Demographic and clinical characteristics of the included patients were investigated in the 12-month period preceding the index date. For the primary outcome, i.e. non-persistence risk within 12 months (follow-up period), the end of the exposure period was determined by therapy discontinuation, switch to a different molecule or add-on of a different molecule into the regimen, whichever occurred first. A patient exceeding the 90-days permissible gap between refilling prescriptions defined discontinuation of therapy. In addition, patients whose last claim occurred 90 days or less before the end of the follow-up were considered persistent throughout the follow-up period. Finally, warfarin use was determined using information from both prescriptions and INR/PT claims. In fact, even when gaps between prescriptions claims were longer than 90 days, we considered the patient to be on drug with warfarin as well in case INR/PT measurements were recorded within the gap duration. Patients were censored at the first event (discontinuation/switch/add-on), death or end of the study (31 December 2015), whichever occurred first. The total number of days on therapy for each molecule was quantified by means of the Defined Daily Dose (DDD). Antiplatelet class was included neither in the persistence analysis nor in the health care resource utilization analyses given the nature of data sources. In fact, LHUs supplied aggregated data on billable claims only and, for this reason, not-reimbursed drugs could not be fully monitored by administrative databases. For the secondary outcome, i.e. health care resource utilization analysis, the all-causes hospitalizations, outpatient visits and examinations requests within the persistence period were also collected.

STATISTICAL ANALYSES

Baseline characteristics, i.e. age, gender, CHA2DS2-VASc score and HAS-BLED score, were summarized as frequencies and percentages (qualitative variables), and as mean and standard deviation (SD) (quantitative variables) and were stratified by treatment class (VKAs, NOACs and antiplatelets). The proportion of patients who were persistent over the course of follow-up was calculated and cumulative incidence curves of non-persistence within 12 months, accounting for the competing risk of death, were presented for both VKAs and NOACs groups. Multivariate Cox regression methods to model time to non-persistence within 12 months were performed; covariates included in the model were the treatment group (NOACs versus VKA), age, sex, CHA2DS2 VASc and HAS-BLED score, and proportionality of hazards was tested. An additional analysis evaluated the primary outcomes with a focus on four molecules of interest (warfarin, apixaban, rivaroxaban, and dabigatran) with patients grouped based on the molecule received. Thus, a second multivariate Cox regression

model was run including, together with the other covariates, a different variable accounting for treatment group, with warfarin being the reference molecule. Finally, the mean number of all-causes hospitalizations, outpatient visits and examinations requests were compared among NOACs versus VKA using 1-sample t test. All the analyses were performed using SAS software, version 9.4.

Results

According to inclusion criteria, we identified 7970 NVAF patients who initiated treatment with an OAC or an antiplatelet. In particular, 2909 patients (36.1%) were treated with VKAs, 765 with NOACs (9.5%) and 4296 with antiplatelet (53.3%). Demographic characteristics were quite similar among the three groups, with a slightly higher proportion of females and older patients observed in the antiplatelet group. High risk of bleeding (HAS-BLED score of ≥ 3) was more observed among antiplatelet patients (34.1%) when compared with OAC users (VKA: 21.2%; NOAC: 18.8%), and the same for stroke risk. In fact, the proportion of patients presenting with a CHA2DS2-VASc score ≥ 2 ranged from 84.7% in the antiplatelet cohort to 80.4% and 78.4% in the NOAC and VKA groups, respectively (table 1).

Cumulative incidence curves of discontinuation for NOACs and VKAs are presented in figure 1 suggesting a better persistence profile of NOAC throughout the follow-up period. In particular, the proportion of 12-months persistent patients was 67.8% among NOAC users and 37.2% among VKA users. Results from the multivariate Cox regression model showed a 62% reduction in risk of drug discontinuation for NOAC patients compared to VKA patients (HR, 0.38 [0.33-0.44]). No other factors affected the risk of discontinuation, except for patients aged 50-64 with a barely significant 19% reduction in risk compared with 80 years or older patients (HR, 0.81 [0.67-0.96]) (table 2). The additional analysis focusing on the four molecules of interest showed a higher persistence at 1 year since drug initiation among apixaban users (n=92; 75.4%), followed by rivaroxaban (n=152; 68.8%), dabigatran (n=275; 65.2%) and warfarin (n=935; 43.3%) patients. Cumulative incidence curves to illustrate the rate of non-persistence over the follow-up time for each molecule are reported in figure 2. Proportional Hazards assumption was verified and results from the Cox regression model showed that all the patients treated with a NOAC molecule had statistically significant lower risk of non-persistence when compared with warfarin (table 3). In particular, as suggested by the highest proportion of 12-month persistent patients, it is worth noticing that apixaban users showed the highest reduction in risk of drug discontinuation (65%) when compared with rivaroxaban and dabigatran users (58% and 49%, respectively). Again, among the covariates considered, only age had a significant effect on the non-persistence with a significant higher

Table 1. Characteristics of the Study Population.

	VKA	NOAC	Antiplatelet
No. of patients	2909	765	4296
Male (n, %)	1518 (52.2)	409 (53.5)	2130 (49.6)
Age (mean, SD)	74.7 (11)	76.4 (9)	77.6 (10)
Age <50 (n, %)	69 (2.4)	10 (1.3)	53 (1.2)
Age 50-64 (n, %)	370 (12.7)	65 (8.5)	399 (9.3)
Age 65-79 (n, %)	1406 (48.3)	381 (49.8)	1777 (41.4)
Age 80+ (n, %)	1064 (36.6)	309 (40.4)	2067 (48.1)
CHA2DS2-VASc score (mean, SD)	2.7 (1)	2.8 (2)	3.0 (2)
CHA2DS2-VASc score <2 (n, %)	628 (21.6)	150 (19.6)	656 (15.3)
CHA2DS2-VASc score ≥2 (n, %)	2281 (78.4)	615 (80.4)	3640 (84.7)
HAS-BLED (mean, SD)	1.8 (1)	1.8 (1)	2.4 (1)
HAS-BLED score <3 (n, %)	2292 (78.8)	621 (81.2)	2830 (65.9)
HAS-BLED score ≥3 (n, %)	617 (21.2)	144 (18.8)	1466 (34.1)

Table 2. Multivariate Cox regression model (ref. VKA) of non-persistence within 12 months – Drug Class.

	HR	95% CI	
		Lower	Upper
Index drug class (ref. category: VKA)			
NOAC (*)	0.38	0.33	0.44
Demographics at baseline			
Female	1.01	0.92	1.11
Age <50 vs Age 80+	1.02	0.76	1.37
Age 50-64 vs Age 80+ (*)	0.81	0.67	0.96
Age 65-79 vs Age 80+	0.98	0.73	1.31
Clinic factors at baseline			
CHA2DS2-VASc ≥2	0.91	0.79	1.05
HAS-BLED ≥3	0.99	0.89	1.11

HR: Hazard Ratio; VKA: vitamin K-antagonist; NOAC: non-vitamin K antagonist oral anticoagulants
 (*) Significant at the 0.05 level.

Table 3. Multivariate Cox regression model (ref. warfarin) of non-persistence within 12 months – Molecule.

	HR	95% CI	
		Lower	Upper
Index molecule (ref. category: warfarin)			
Dabigatran (*)	0.51	0.43	0.61
Rivaroxaban (*)	0.42	0.33	0.54
Apixaban (*)	0.35	0.24	0.50
Demographics at baseline			
Female	1.02	0.91	1.14
Age <50 vs Age 80+	1.05	0.75	1.46
Age 50-64 vs Age 80+ (*)	0.71	0.57	0.89
Age 65-79 vs Age 80+ (*)	0.80	0.71	0.90
Clinic factors at baseline			
CHA2DS2-VASc ≥2	0.85	0.71	1.00
HAS-BLED ≥3	0.98	0.86	1.12

HR: Hazard Ratio; (*) Significant at the 0.05 level.

risk among the elderly (age 80+) compared with patients aged 50-64 (HR, 0.71 [0.57-0.89]) and 65-79 (HR, 0.80 [0.71-0.90]). Health care resource utilization analysis showed that, independently from treatment class at index date, the majority of 12-month persistent patients (n=1.601) had at least one outpatient visit and examinations request within the persistence period

(69.2% and 98.4% of incident users, respectively). A slightly higher percentage of VKA patients returned at least one of the abovementioned health care resource utilization parameters when compared with NOAC users (figure 3). All-cause hospitalizations were found in 356 of 1082 VKA patients (32.9%) and in 147 of 519 NOAC patients (28.3%). Mean total numbers of all-

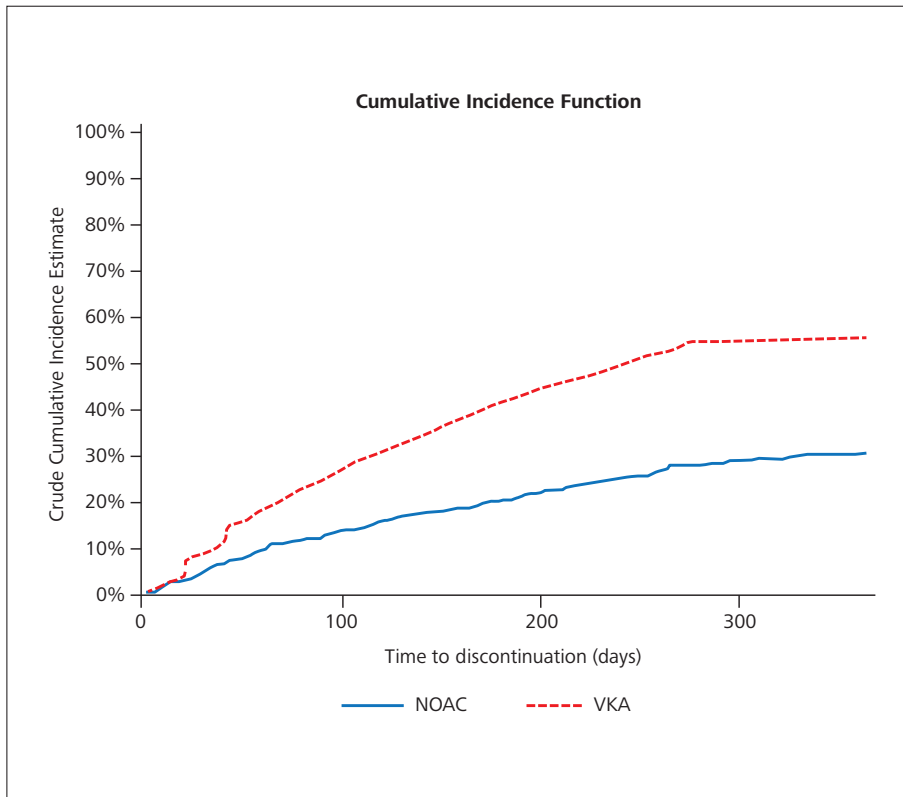


Figure 1. Cumulative incidence of non-persistence according to drug class at Index Date taking into account competing risk of death.

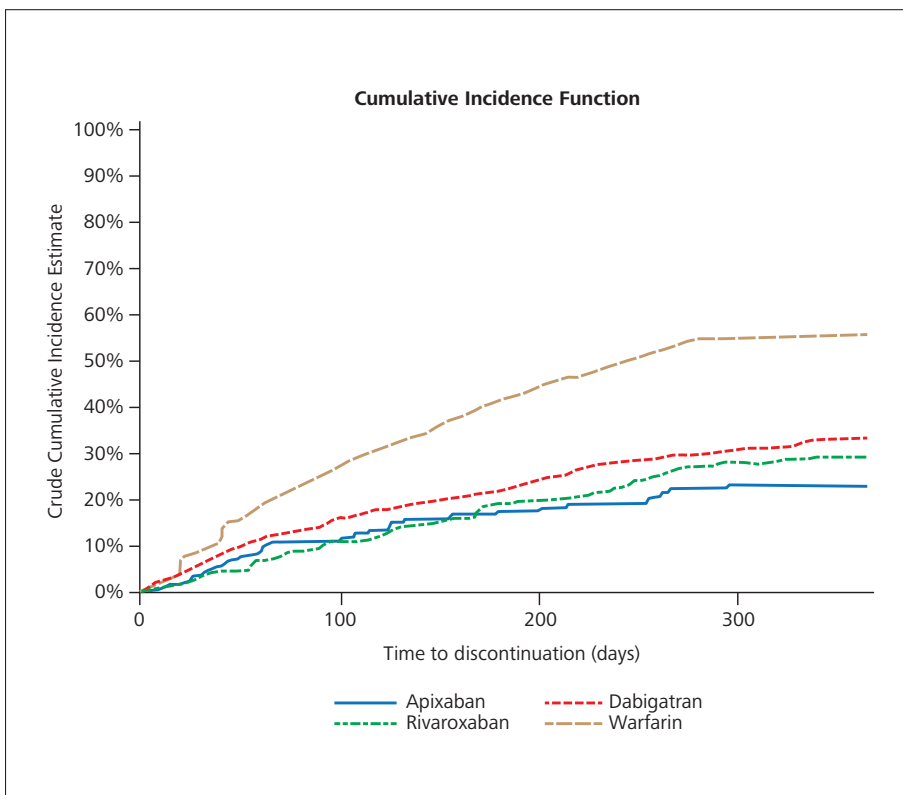


Figure 2. Cumulative incidence of non-persistence according to the molecule prescribed at the Index Date taking into account competing risk of death.

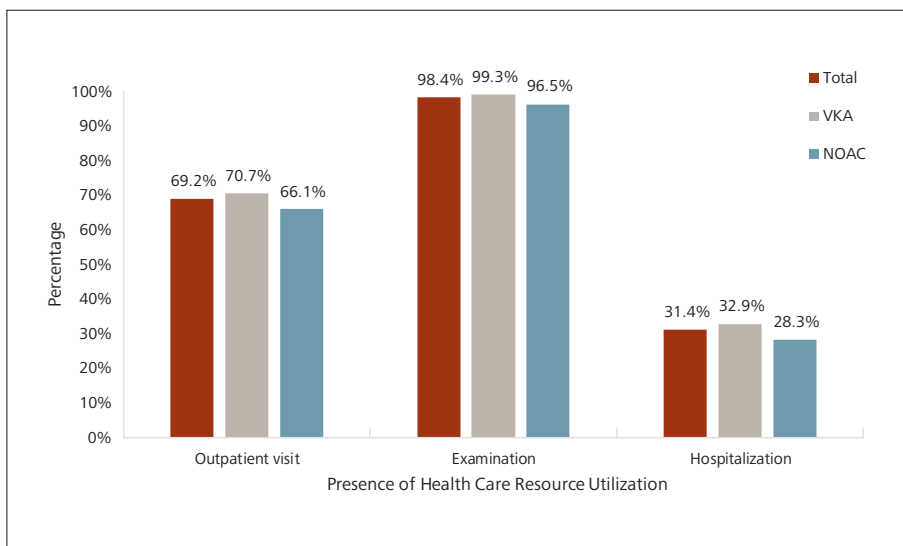


Figure 3. Percentage of 12-month persistent patients with at least one hospitalization, outpatient visit and examination request (Total, VKA and NOAC users).

cause hospitalizations records were significantly less in NOACs users compared with VKA users (0.36 vs 0.47, p-value: 0.01). Similarly, the differences in the mean numbers of all-cause outpatient visits and examinations were statistically significant between VKA and NOAC patients, who registered on average 2.33 vs 1.84 visits (p-value: 0.0002) and 24.4 vs 9.2 exams referrals (p-value: <.0001), respectively (table 4).

Discussion

The major finding emerging from the present study is the better profile of NOAC patients compared with VKA users in terms of: 1) non-persistence risk within 12 months 2) health care resource consumption within the persistence period.

Poor persistence with VKAs, in particular with warfarin, was already assessed by previous studies worldwide: an Australian study by Simons et al.³⁰ found that 62% of warfarin patients discontinued the treatment within 12 months compared with 30% of NOAC patients, thus being in strong agreement with our findings returning 62.8% and 32.2% of discontinuation among VKA and NOAC users, respectively. A Spanish retrospective study using similar methodology to ours found that VKA drugs were the most prescribed treatments and, at the same time, the ones returning the shortest persistence among newly diagnosed NVAF patients at the first-line of therapy³¹. However, it is worth mentioning that results on persistence at one year since treatment start in our study are quite low when focusing on warfarin. In fact, even if similarly to previous studies³²⁻³⁴, we in-

Treatment at Index Date	Number of Health Care Resources	Health Care Resource Utilization		
		Mean Number	Std Dev	Pr > t
Outpatient Visit				
NOAC	955	1.84	0.09	0.0002
VKA	2524	2.33	0.09	
Laboratory Examination				
NOAC	4796	9.24	7.90	<.0001
VKA	26347	24.35	16.59	
Hospitalization				
NOAC	189	0.36	0.66	0.0058
VKA	507	0.47	0.80	

Std Dev: Standard Deviation.

cluded INR/PT measurements as a proxy of warfarin fills, the proportion of warfarin patients that was persistent at one year since treatment start is still low. A recent UK study by Johnson et al.³⁵ assessed an overall persistence of 70.6% among warfarin patients that is much higher than the 43% observed in the present study. A possible explanation is that, in the UK study, when calculating VKA persistence, the median duration observed for VKA prescriptions was added as many times as the number of INR records found. In addition, also a 30-day grace period was added to the end of the treatment line. Differently, in the present study, INR/PT records did not account for additional days of persistence and grace periods were not considered. In conclusion, despite discrepancies in the magnitude of persistence values potentially due to the different methodologies used, the high non-persistence risk assessed among VKA patients is in line with the recent European literature³⁶⁻³⁸, as well as with those studies reporting discontinuation at one year in more than 1 out of 4 patients^{26,39,40}. In recent years, and precisely since the introduction of multiple NOACs, the interest in comparing persistence among these new drugs has considerably grown. In this respect, another important result from the present study is the higher reduction in the risk of drug discontinuation observed for apixaban when compared to rivaroxaban and dabigatran. Accordingly, indications of improved persistence rates with apixaban over the other OACs emerged from recent real-world studies based on administrative and claims database in Denmark⁴¹, Sweden⁴², US⁴³ and Italy²⁹.

To our knowledge, very few studies attempted to compare health care resource utilization between NOAC and VKA users. In addition, these studies were mostly focused on specific molecules, rather than on classes of treatment. Two recent studies performed in US and Canada and based on administrative health care claims databases compared dabigatran vs warfarin and rivaroxaban vs warfarin, respectively^{44,45}. The main outcomes considered were the mean number of all-cause hospitalizations and outpatient visits. Both the two NOACs showed a lower resource utilization with respect to warfarin and this has been confirmed by our findings but from a treatment class-level point of view. In addition, the almost 3-folds higher mean number of laboratory tests associated with VKAs when compared with NOACs from the present study also confirm the well-known necessity of frequent and long-term laboratory monitoring required for warfarin patients⁴⁶, which has also recently promoted NOACs as a cost-saving alternative to VKAs⁴⁷.

The main strength of the present study is the validity of the overarching source of information used. Administrative databases indubitably represent a valuable source for recording and monitoring consumptions that are at the expense of the Italian NHS National Health Service (Servizio Sanitario Nazionale - SSN), as they give information on most services provided in a healthcare environment^{29,44}. Furthermore, conducting studies based on secondary-data is the

suitable approach for assessing important outcomes in the real world setting. Under this perspective, claims databases are the most proper source of data for estimating AF management and treatment patterns also allowing to control for potential systematic differences between treatment groups in terms of patients characteristics or clinic prognostic factors.

Nevertheless, the study also presents some limitations, typical of the real world evidence studies. First, treatment exposure is based on prescribed and dispensed prescriptions by pharmacies and no information on actual use of the drugs is available. Second, stroke, as well as bleeding risk at baseline, was assessed through the hospitalization discharge forms; for this reason, only patients requiring an hospitalization, i.e. the most severe cases, were included in the CHA2DS2-VASc and HAS-BLED score definition. Third, the unavailability of INR values together with the impossibility of assessing dose adjustments did not allow for an accurate estimation of days of persistence for warfarin patients. In fact, an out-of-range INR value could imply an adjustment in treatment dosage that cannot be well detected when calculating treatment duration based on DDD. Finally, we focused on patients who are naïve to the OACs molecule considered in each treatment group, whilst different results could have been obtained including patients that are naïve for the entire OACs class.

Conclusions

Our study provides important real-world insights in a large cohort of Italian patients confirming both the higher medium-term persistence rates and the lower

Take-home messages.

- Very little was known about the Italian experience about non-persistence rates and healthcare resource utilization with VKA-treated users compared with NOACs.
- In a large cohort of Italian patients, the proportion of 12-months persistent patients was 67.8% among NOAC users and 37.2% among VKA users. Results from the multivariate Cox regression model showed a 62% reduction in risk of drug discontinuation for NOAC patients compared to VKA patients.
- Among NOAC drugs, apixaban presented the lowest risk of discontinuation compared with dabigatran and rivaroxaban.
- Mean total numbers of all-cause hospitalizations records, all-cause outpatient visits and examinations referrals were significantly less in NOACs users compared with VKA users.
- The present study has provided valuable additional evidence that supports both the higher medium-term persistence rates and the lower healthcare resource consumption of NOACs compared with VKAs.

healthcare resource consumption of NOACs compared with VKAs. Among NOAC drugs, apixaban presented the lowest risk of discontinuation compared with dabigatran and rivaroxaban. Future studies allowing for a longer follow-up since apixaban commercialization should be encouraged to evaluate whether results from the present study could be extended to a long-term evaluation.

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