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Non-vitamin K antagonist oral anticoagulation agents in patients with atrial fibrillation: Insights from Italian monitoring registries

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ABSTRACT

Background: Atrial fibrillation (AF) is the most common cardiac arrhythmia associated with an increased risk of stroke and thromboembolism. Anticoagulation with Vitamin K antagonists (VKAs) or with novel oral anti-coagulants (NOACs) represents the cornerstone of the pharmacological treatment to reduce the risk of thromboembolism. This study aims to provide real-world data from a whole large European country about NOAC use in "non-valvular atrial fibrillation" (NVAF).

Methods: We analysed the Italian Medicines Agency (AIFA) monitoring registries collecting data of a nationwide cohort of patients with "NVAF" treated with NOACs. Using logistic regression analysis, baseline characteristics and treatment discontinuation information were compared among initiators of the 4 NOACs.

Results: In the reference period, the NOAC database collected data for 683,172 patients. The median age was 78 years with 19.5% aged 85 or older. Overall, the treatments were in accordance with guidelines. About 1/3 of patients switched from a prior VKA treatment; in the 72.3% of cases, these patients had a labile International Normalized Ratio (INR) at first prescription. The most prescribed NOAC was rivaroxaban, followed by apixaban, dabigatran and edoxaban.

Conclusions: This study is the largest European real-world study ever published on NOACs. It includes all Italian patients treated with NOACs since 2013 accounting for about 1/3 of subjects with AF. The enrolled population consisted of very elderly patients, at high risk of ischemic adverse events. The AIFA registries are consolidated tools that guarantee the appropriateness of prescription and provide important information for the governance of National Health System by collecting real-world data.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and it is associated with increased morbidity and mortality, especially in older age groups [1]. Due to the progressive aging of population, AF will become one of the major causes of stroke, heart failure, sudden death, and cardiovascular morbidity in the world with a rising global burden for National Health System (NHS) and society [2,3].

According to dedicated guidelines, pharmacological treatment of this arrhythmia includes anticoagulant agents to reduce the risk of stroke and thromboembolism [4].

Before the introduction of novel oral anticoagulants (NOACs), Vitamin K antagonists (VKAs) were the standard therapy to prevent thromboembolism. Nevertheless, the use of NOAC agents has been encouraged by a better benefit/risk profile, fewer interactions compared with VKAs and no need for routine coagulation monitoring [5]. Current treatment guidelines state that oral anticoagulant (OAC) therapy to prevent thromboembolism is recommended for all male AF patients with CHA_2DS_2-VASc score of 2 or more and in all female with CHA_2DS_2-VASc score of 3 or more [4]. When OAC is initiated in a patient with AF who is eligible for NOACs, these medicines are recommended in preference to VKA.

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At national level, the Italian Medicines Agency (AIFA) established that NOACs can be prescribed and reimbursed only in presence of specific requirements such as suboptimal international normalized ratio (INR) control with VKA or objective difficulties in carrying out the periodic monitoring. In Italy, it is mandatory to perform NOACs prescription through web-based monitoring registries, which represent one of the instruments adopted by NHS in order to manage budget impact, uncertain clinical outcome, and appropriate use of medicines.

This study aims to provide real-world data collected in the AIFA database of monitoring registries, describing a nationwide cohort of patients with "non-valvular atrial fibrillation" (NVAF) treated with NOAC therapy and factors associated with treatment choice. Our analysis provides unique epidemiological information of whole and unselected population of patients treated with NOACs in a large European country. Furthermore, it provides interesting data on the appropriateness of treatment choice, the characteristics of the patients, those who discontinued or switched medications and on changing patterns of prescriptions in the last 5 years.

2. Methods

We included all patients with "non-valvular atrial fibrillation" (NVAF) who were prescribed a NOAC through AIFA registries, between June 16, 2013 (date of Italian approval of the first NOAC) and December 31, 2017. The treatment indication has been given by authorized clinicians who identified, during daily clinical practice, "NVAF" patients candidate to NOAC on the base of current guidelines.

The AIFA database collects the information required for NOAC prescription and reimbursement by Italian NHS. This obligation, as established by the Italian laws, does not require any consent form. However, upon inclusion in the system, each patient receives information about the purposes of the procedure.

NOACs monitoring registries are made of specific data entry forms, filled in by authorized clinicians: *i)* registration form with patient personal data (anonymised after registration); *ii)* eligibility and clinical data form; *iii)* prescription form; i*v)* re-evaluation of disease status and treatment update form and *v)* end-of-treatment form. Re-evaluation and end-of-treatment forms provide main safety and effectiveness data for each patient. Each prescription has one-year validity and might be renewed at the expiration upon a mandatory re-evaluation.

The online deployment of the 4 registries followed Italian approval of NOACs: June 2013 for dabigatran, August 2013 for rivaroxaban, December 2013 for apixaban, and August 2016 for edoxaban. Therefore, patients were consecutively included in the database for a period ranging from a minimum of 16 months (treatment with edoxaban) to a maximum of more than 5 years (treatment with dabigatran).

2.1. Statistical analysis

Data were analyzed using the statistical software R. The R libraries ggplot2 [6] and circlize [7] have been used for data visualization. The Chi-square and Kruskal–Wallis were adopted for categorical and continuous variable respectively considering a P-value of 0.05 statistically significant.

We determined factors associated with the prescription of each NOAC against the others, using multivariate logistic regression performed with SAS 9.4. The baseline characteristics of patients filled out in the clinical data form to check eligibility were included in the models to obtain the corresponding adjusted odds ratios (ORs).

A similar strategy has been adopted to calculate the adjusted ORs for the 12 months discontinuation and the switches among drugs. In this case, we selected a subset of the entire population, enrolled in the third trimester of 2016, to include all the 4 NOACs in the analysis, and observed the number of renewals performed at the end of the first 12-month prescription or the number of patients that changed to a different NOAC. "Lost to follow-up" was defined as a treatment with the last prescription expired from at least 6 months.

The logistic regression performed for evaluating the odds of discontinuation and switch within 12 months of treatment took into consideration all the available baseline characteristics. In particular, we reported age, $CHAD_2DS_2$-VASc and HAS-BLED score as categorical variables and the other covariates as dichotomous.

To evaluate the 24-month switches, we did not consider any patient registered before 2015 in order to avoid possible bias due to the different dates of authorization of the three NOACs available in that period. Eventually, we described the differences in the populations that started their treatments in 2014 and 2017 respectively, investigating the changes in the relative frequencies of specific subgroups.

3. Results

From June 2013 to December 2017, the AIFA NOAC registries collected data for 683,172 patients, corresponding to a total of 725,690 started treatments. This nationwide cohort includes all Italian patients with NVAF treated with NOACs, except those from the Emilia Romagna Region.

3.1. Characteristics of the cohort

Table 1 shows baseline characteristics according to NOAC treatment. The median age was 78 years (range 18–109 years) with 19.5% of patients aged 85 and older. Male gender was slightly prevalent compared to female ones (50.1% versus 49.9%). Mean CHA_2DS_2-VASc and HAS-BLED score were respectively 4.0, and 2.5. Overall, 93% (675743) of patients had a CHA_2DS_2-VASc score of 2 or more (if male) or of 3 or more (if female). More than 80% of population has a HAS-BLED score less than 4.

About 1/3 (33.7%) of patients switched to NOACs from a prior VKA treatment and among these 72.3% had a labile INR at first prescription.

Overall, the most prescribed NOAC in naïve and switched patients was rivaroxaban (33.8% of treatments) followed by apixaban (31.1%), dabigatran (28.6%) and edoxaban (6.5%).

Comparison between baseline characteristics of population who started treatment in 2014 (n = 121728) versus 2017 (n = 216331) is reported in Supplementary Table 1. Patients enrolled in 2014 had more frequently a history of prior anticoagulant treatment (45.9% versus 22.2%), mostly with labile INR, concomitant use of medications predisposing to bleeding (non steroidal anti inflammatory drugs, NSAIDs, 19.5% versus 15.2%) and higher risk of thromboembolic and hemorrhagic events compared to those enrolled in 2017. On the other hand, more patients enrolled in 2017 were 85 years or older (17.4% versus 21.7%).

3.2. Treatment initiation trends

Monthly initiation trend is reported in Supplementary Fig. 1. We observed a strong increase in the number of new treatments (naïve and switch) for each NOAC in the first six months after marketing release (+33226 new treatments for dabigatran, +15525 for rivaroxaban, +10779 for apixaban and +10984 for edoxaban). Dabigatran had a stable trend during the last whole period of observation (average number of new treatments per months equal to almost 3680 in 2014 and 3700 in 2017), while apixaban and

Table 1
Baseline characteristics according to NOAC treatment.

	Apixaban	Edoxaban	Dabigatran	Rivaroxaban	Overall
N° of treatments (%)	225,457 (31.1)	47,397 (6.5)	207,252 (28.6)	245,584 (33.8)	725,690 (1 0 0)
Female (%)	118,703 (52.7)	24,850 (52.4)	97,416 (47)	122,722 (50)	363,691 (50.1)
Male (%)	106,754 (47.4)	22,547 (47.6)	109,836 (53)	122,862 (50)	361,999 (49.9)
MedianAge (range),	79 (18–109)	79 (18–104)	77 (18–102)	78 (18–106)	78 (18–109)
<65 (%)	18,068 (8)	4366 (9.2)	25,545 (12.3)	27,718 (11.3)	75,697 (10.4)
≥ 65 & <75 (%)	52,836 (23.4)	11,512 (24.3)	60,683 (29.3)	63,893 (26)	188,924 (26)
≥ 75 & <85 (%)	100,570 (44.6)	20,180 (42.6)	90,752 (43.8)	107,778 (43.9)	319,280 (44)
≥ 85 (%)	53,983 (23.9)	11,339 (23.9)	30,272 (14.6)	46,195 (18.8)	141,789 (19.5)
Vascular disease history (%)	62,967 (27.9)	12,204 (25.8)	54,882 (26.5)	66,987 (27.3)	197,040 (27.2)
CHF history (%)	68,616 (30.4)	13,334 (28.1)	53,520 (25.8)	73,923 (30.1)	209,393 (28.9)
Hypertension history (%)	194,215 (86.1)	40,710 (85.9)	180,062 (86.9)	212,611 (86.6)	627,598 (86.5)
Diabetes history (%)	45,508 (20.2)	8947 (18.9)	41,215 (19.9)	48,471 (19.7)	144,141 (19.9)
Stroke/TIA/Thromboembolism history (%)	44,686 (19.8)	7213 (15.2)	39,023 (18.8)	41,835 (17)	132,757 (18.3)
Liver disease (%)	2302 (1)	380 (0.9)	2209 (1.1)	2190 (0.9)	7081 (1)
Renal disease (%)	17,013 (7.6)	3138 (6.6)	5987 (2.9)	13,185 (5.4)	39,323 (5.4)
Alcohol use (%)	10,575 (4.7)	2678 (5.7)	10,533 (5.1)	11,036 (4.5)	34,822 (4.8)
Prior major bleeding or predisposition to bleeding (%)	31,597 (14)	5060 (10.7)	22,546 (10.9)	24,247 (9.9)	83,450 (11.5)
Prior anticoagulant treatment (VKA) (%)	63,692 (28.3)	11,191 (23.6)	81,189 (39.2)	80,522 (32.8)	236,594 (32.6)
Labile INR (%)	46,634 (20.7)	7823 (16.5)	57,282 (27.6)	59,802 (24.4)	171,541 (23.6)
Medication usage predisposing to bleeding (%)	37,880 (16.8)	6710 (14.2)	38,238 (18.5)	41,382 (16.9)	124,210 (17.1)
Prior NOAC treatment (switch) (%)	19,906 (8.8)	4952 (10.5)	4200 (2)	13,272 (5.4)	42,330 (5.8)
CHA_2DS_2-VASc Score 0 (%)	864 (0.4)	210 (0.4)	1390 (0.7)	1965 (0.8)	4429 (0.6)
CHA_2DS_2-VASc Score 1 (%)	6680 (3)	1706 (3.6)	9223 (4.5)	10,271 (4.2)	27,880 (3.8)
CHA_2DS_2-VASc Score 2 (%)	21,554 (9.6)	5353 (11.3)	26,295 (12.7)	27,838 (11.3)	81,040 (11.2)
CHA_2DS_2-VASc Score 3 (%)	45,719 (20.3)	10,564 (22.3)	47,895 (23.1)	52,653 (21.4)	156,831 (21.6)
CHA_2DS_2-VASc Score 4 (%)	62,803 (27.9)	13,545 (28.6)	55,386 (26.7)	67,486 (27.5)	199,220 (27.5)
CHA_2DS_2-VASc Score 5 (%)	45,140 (20)	8786 (18.5)	35,984 (17.4)	45,567 (18.6)	135,477 (18.7)
CHA_2DS_2-VASc Score 6+ (%)	42,697 (18.9)	7233 (15.3)	31,079 (15)	39,804 (16.2)	120,813 (16.7)
HAS-BLED Score 0 (%)	2893 (1.3)	761 (1.6)	4130 (2)	5007 (2)	12,791 (1.8)
HAS-BLED Score 1 (%)	27,876 (12.4)	7422 (15.7)	29,844 (14.4)	34,048 (13.9)	99,190 (13.7)
HAS-BLED Score 2 (%)	89,107 (39.5)	20,935 (44.2)	78,147 (37.7)	98,932 (40.3)	287,121 (39.6)
HAS-BLED Score 3 (%)	65,475 (29)	11,813 (24.9)	60,480 (29.2)	68,563 (27.9)	206,331 (28.4)
HAS-BLED Score 4+ (%)	40,106 (17.8)	6466 (13.6)	34,651 (16.7)	39,034 (15.9)	120,257 (16.6)

CHF = congestive heart failure; CHA_2DS_2-VASC = congestive heart failure, hypertension, age ≥ 75 [doubled], diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65–74, female; HAS-BLED = hypertension, abnormal renal and liver function, stroke, bleeding, labile INR, elderly, drugs or alcohol abuse; INR = international normalized ratio; TIA = transient ischemic attack; VKA = Vitamin K Antagonist.

rivaroxaban rapidly exceed dabigatran in terms of new prescriptions and became the preferred choices (average number of new treatments per months went from almost 2640 in 2014 to 5600 in 2017 for apixaban, and from almost 3820 in 2014 to 5170 in 2017 for rivaroxaban).

Even edoxaban exhibited a strong positive prescription trend in the first six months after marketing authorization despite being the last NOAC available in the late 2016. Noteworthy in the same period we observed a reduction in the number of new treatments with rivaroxaban (−9.4% compared to the mean of the reference period).

3.3. Factors associated with treatment choice

Different factors affected the choice of a specific NOAC in the monitored population (Fig. 1 and Table 1). In the oldest group, dabigatran was the least prescribed (OR 0.63, 95% CI 0.60–0.66), in favor of apixaban and edoxaban (respectively 1.52, 95% CI 1.46–1.59 and 1.6, 95% CI 1.47–1.74). A CHA_2DS_2-VASc score equal to 3 or higher was more strongly associated with apixaban or dabigatran use with an OR for the 6 + class of 1.42 (95% CI 1.24–1.62) and 1.36 (95% CI 1.18–1.56), respectively. The opposite pattern was seen in the rivaroxaban group (OR 0.57, 95% CI 0.50–0.65 for the 6 + class). The choice of all NOACs was also affected by a HAS-BLED score higher than 4, with a higher frequency of prescription for apixaban and rivaroxaban (OR 1.43, 95% CI 1.34–1.54 and 1.23, 95% CI 1.15–1.31 respectively) and lower for edoxaban and dabigatran (OR 0.78, 95%bCI 0.69–0.88 and 0.59, 95% CI 0.55–0.63 respectively).

Prescription of dabigatran was more frequent in case of abnormal liver function (OR 1.40, 95% CI 1.33–1.48), while apixaban (OR 1.48, 95% CI 1.44–1.51) and edoxaban (OR 1.35, 95% CI 1.29–1.41) were preferred in case of renal disease. Prior treatment with VKA was strongly associated with dabigatran (OR 1.53, 95% CI 1.51–1.56) as well as the concomitant use of medications predisposing to bleeding, such NSAIDs (OR 1.34, 95% CI 1.31–1.36).

3.4. Treatment discontinuation and switches among drugs

Overall, the date of end of treatment or switch was available for 50.345 treatments (7% of all treatments) while the number of lost to follow-up was 189.890 (26%). Therefore, the total number of discontinued and closed treatments was equal to 240.235 (33%). Unfortunately, no information was available for the patients lost to follow-up.

We analyzed treatment discontinuation taking into account naïve patients who started their treatment between September and November 2016 (n = 40575) in order to include subjects with a follow up period of at least 12 months for all NOACs (Table 2a).

Small differences in the odds of discontinuation were found for edoxaban and dabigatran (OR 1.2, 95% CI 1.07–1.33 and 1.1, 95% CI 1.04–1.17, respectively) compared to apixaban.

The likelihood of discontinuation within 12 months was higher in patients aged 85 years or older compared to the youngest groups (OR 1.74, 95% CI 1.43–2.11 versus <65 years, see the Supplementary Table S2). The increase of CHA_2DS_2-VASc did not affect the odds of a renewal; however, the lowest scores (0 and 1) showed a higher odds of end of treatment compared to the others. Finally, presence of diabetes, congestive heart failure (CHF) or renal disease

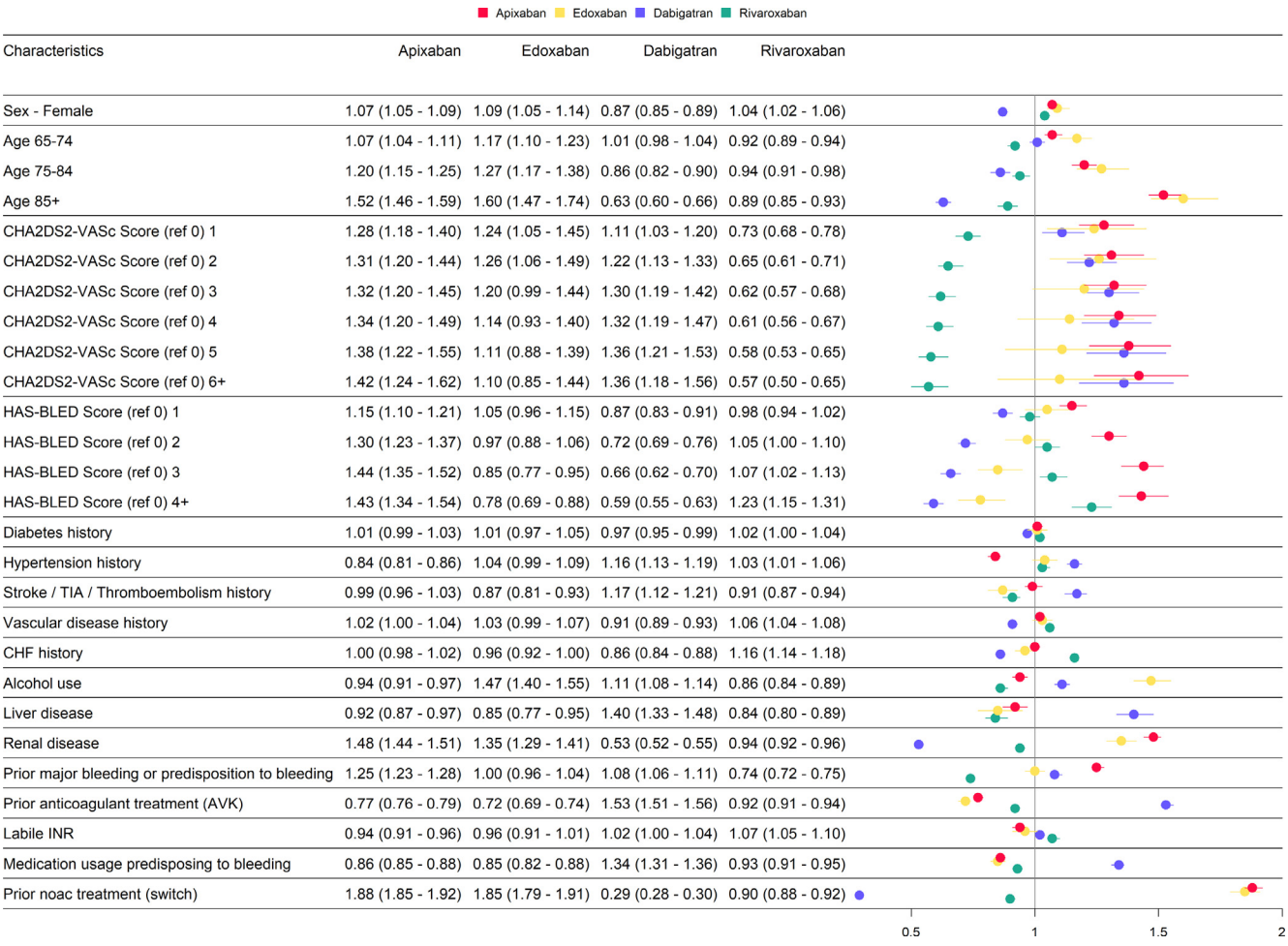

Fig. 1. Odds ratios (ORs) and theirs 95% confidence intervals for NOAC choice according to the baseline characteristics resulting from the multivariate logistic regression models. The specific population of each drug has been compared with the remaining patients treated with the other NOACs. ORs and their 95% confidence intervals are colored in red, yellow, purple and turquoise respectively for apixaban, edoxaban, dabigatran and rivaroxaban.

Table 2a
Risk of discontinuation within 12 months among NOACs.

	OR (95% CI)	p-value	Lost to follow up – N (%)	Treatments (N)
Apixaban	1		4044 (26.3)	15,366
Edoxaban	1.19 (1.07–1.33)	0.0018	527 (27.9)	1892
Dabigatran	1.10 (1.04–1.17)	0.0022	2290 (23.9)	9584
Rivaroxaban	1.02 (0.97–1.08)	0.4294	3441 (25.1)	13,733
All NOACs			**10,302 (25.4)**	**40,575**

increased the odds of discontinuation (OR 1.25, 95% CI 1.14–1.37; 1.57, 95% CI 1.43–1.71; 1.30, 95% CI 1.16–1.46, respectively). On the contrary a prior treatment with VKA was associated with a higher frequency of renewal of prescription (OR for discontinuation 0.66, 95% CI 0.60–0.72).

Table 2b shows the odds of switching in the same population. Compared to apixaban, there was an increased likelihood of switching for all the other NOACs, in particular almost five times higher for dabigatran (OR 4.73, 95% CI 4.07–5.51).

From January 2015, a total of 16,967 out of 486,215 patients (3.5%) treated with dabigatran, rivaroxaban or apixaban switched to another of these drugs. The number and percentage of inter-NOAC switches are reported in Supplementary Table S3, considering three different time windows (switch within 12, 18 and 24 months). About three out of four switches take place within 12 months (mean 8.5 months; median 6 months). The total number of patients with at least one switch up to 24 months was 15,799 (3.3%) patients. More than half of switches came from dabigatran (32% in favor of apixaban and 22% in favor of rivaroxaban, Fig. 2). Switches from rivaroxaban amounted to about 31%, including 21.5% to apixaban and 8.9% to dabigatran. Globally apixaban resulted the NOAC with the smallest switch percentage and the highest number of patients with a previous NOAC treatment (overall 15%, 9.3% to rivaroxaban and 6.4% to dabigatran).

4. Discussion

The AIFA monitoring registries have been introduced in 2005 and represent an advanced online tool to ensure the appropriateness of prescriptions and control pharmaceutical expenditure, even through the application of Managed Entry Agreements (MEAs).

Table 2b
Risk of switching within 12 months among NOACs.

	OR (95% CI)	p-value	Switches – N (%)	Treatments (N)
Apixaban	1		262 (1.7%)	15,366
Edoxaban	1.54 (1.13–2.08)	0.0059	55 (2.9%)	1892
Dabigatran	4.73 (4.07–5.51)	<0.001	748 (7.8%)	9584
Rivaroxaban	1.8 (1.53–2.12)	<0.001	411 (3.0%)	13,733
All NOACs			**1476 (3.6%)**	**40,575**

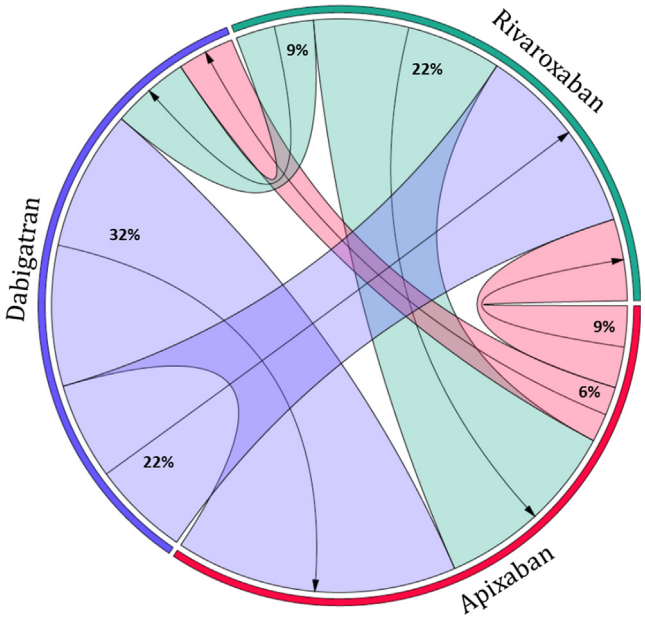

Fig. 2. Circle plot of the up to 24 months switch flow for a subset of the entire population. All patients treated with apixaban (red), dabigatran (purple) or rivaroxaban (turquoise) and with at least one switch in the reference period were included in the analysis.

AIFA registries have been developed for drugs that need a strict control of prescriptions and data collection according to Competent Authority, such as NOACs.

Our study included 683,172 patients, corresponding to a total of 725,690 started treatments (considering that some patients switched among drugs), collected from June 2013 to December 2017 in the AIFA NOAC database. It provides real-world data on NOAC use and persistence in patients with "NVAF". As far as we know, this is the largest database ever published on NOACs in Europe. Assuming a prevalence of AF of approximately 1.9% at the time of approval of NOACs in Italy and an annual incidence of 0.4% [8,9], we could estimate that more than one-third of nearly 2 million Italian patients with AF were treated with NOACs in the last 5 years. These data suggest the wide utilization of NOACs in Italy.

In comparison with previous nationwide registries and real-world studies [5,10–15], the AIFA registries collected data on the oldest population on NOACs ever published (median age 78 years - males 77 years, females 80 years -, 19.5% aged 85 and older), almost equally distributed between males and females, with high rates of co-morbidities and risk of events.

Furthermore, as already described in the observational study of Staerk et al. [10], we found a further significant increase of mean age of patients on treatment from 2014 to 2017, being more than 20% aged at least 85 years old in the last year of observation.

The suboptimal OAC treatment of elderly patients has been subject to increased focus in recent years, since they are at particular high risk of stroke [16–18]. The consistent and large body of evidence in support of the favourable clinical benefit/risk profile of NOACs also in patients at the highest risk, together with the increasing personal experience of specialists, were probably the main reasons explaining the progressive aging of patients treated with NOACs. It has to be underlined that this process seems to have been conducted with specific attention to safety, as the extension of treatment to octogenarians was associated to a selection of patients at a relatively lower thromboembolic and hemorrhagic risk.

According to recent European guidelines [4] OAC therapy to prevent thromboembolism is recommended for all male AF patients with CHA_2DS_2-VASc score of 2 or more and in all female with CHA_2DS_2-VASc score of 3 or more. More than 90% of the Italian patients were treated accordingly to these recommendations. Noteworthy, a previous debate on the inadequacy of Italian limitations for NOAC prescription related to the strict threshold set for the HAS-BLED score [19], can now be overcome on the light of this national wide analysis, which shows that more than 80% of monitored population had a HAS-BLED less than 4. Different criteria were used for declaring eligible these patients, despite their HAS-BLED score.

Overall, the most prescribed NOAC in AIFA registry was rivaroxaban (33.8% of treatments) followed by apixaban (31.1%), dabigatran (28.6%) and edoxaban (6.5%), which was the last one approved. Pattern of prescription for each drug was similar to that reported by others [10,20–22]. The availability of idarucizumab as the only available NOAC reversal agent [23] did not significantly changed the trend of prescription of dabigatran since its authorization in February 2017. Despite being the last NOAC to be available in the late 2016, edoxaban exhibited a strong positive prescription trend in the first six months after marketing authorization, corresponding to a reduction of new rivaroxaban treatments in the same period.

Different factors affected the choice of NOACs in the observed population. Oldest patients were preferably treated with apixaban or edoxaban. For the former, similar conclusions were also reported in previous observations [10]. Similarly, other studies [21,24], demonstrated that patients treated with apixaban, in comparison with dabigatran, were older, with greater proportions of clinical comorbidities and higher stroke and bleeding risk scores, whereas those on rivaroxaban showed an intermediate clinical profile between apixaban and dabigatran. However, these studies did not include edoxaban due to the different time of marketing authorization.

Although there is evidence for a significantly higher persistence rates with NOACs than with VKAs, discontinuation is still a relevant issue for patients on NOACs ranging from 15 to 30% rate, both in real world studies and randomized-controlled trials [25–29].

The discontinuation rate of about one fourth of patients at 1 year observed in our study is in line with previous observations [26,27], especially considering our population of very elderly patients at high risk of events. An increased risk was detected in very elderly, in those at risk of bleeding, in presence of diabetes, congestive heart failure and renal disease, factors previously associated to a higher likelihood of discontinuation [25,30]. On the contrary a prior treatment with VKA was associated with a higher

frequency of renewal of prescription. The odds of discontinuation (whatever the reasons, including treatment interruption, shift to VKA or death) here observed was similar for all NOACs, with a slightly better persistence shown by apixaban and rivaroxaban. In previous studies higher persistence was seen for apixaban and rivaroxaban compared to dabigatran [21,26,30,31]. Unfortunately, since filling information about drug suspension was not mandatory, it was not possible to describe the reasons of discontinuation in our population, making difficult to infer any conclusion. The occurrence of cardiovascular events, mainly bleeding complications, side effects (e.g. dyspepsia), changes in laboratory values (e.g. creatinine clearance), or physicians' or patients' preference towards a specific treatment regime, were the most frequent reasons of non-persistence on treatment in previous experiences [25,26,32] and have been reported to differ among single NOAC agents [21,26]. Compared to data from the literature [33,34], we found a lower rate of switch from one NOAC to another (3.3% of patients), mainly in the first year of treatment. In line with previous reports, apixaban was the less associated with switching, with the highest probability being for dabigatran [35]. Recently, data from a post authorization study performed in order to assess the risk of major bleeding with apixaban, dabigatran and rivaroxaban were published by the European Medicines Agency (EMA) highlighting different safety profiles for the three NOACs [36]. These results could provide an explanation for the wide differences on the switch probabilities here observed. Unfortunately, without knowing the cause of the switches we could not come to any conclusion.

5. Strengths and limitations of the study

It has to be recognized that our study is the largest ever published in the literature on NOAC use including all but one Region of a large European Country. The characteristics of this population, the oldest ever published to the best of our knowledge, express a large access to care and prescription in Italy. Even if Italian monitoring registries represent a tool aiming at manage drug prescription and reimbursement, they allow to perform analysis on clinical data, not feasible with other administrative databases. Nevertheless, some limitations do exist.

The peculiarity of Italian web-based registries, consisting of a mandatory therapeutic plan required for strict control of prescriptions and the absence of a supervised monitoring of data entry and audit visits, could have negatively influenced the quality and accuracy of clinical data. Moreover, we did not have some information important for clinical assessment at baseline and/or follow-up visits such as body mass index, smoking, haemoglobin, severity of renal and hepatic impairment, exact alcohol consumption, and blood pressure values.

Finally, data about drug suspension could be missing, since filling in the end-of-treatment form is not mandatory. Therefore, it was not possible to analyze the causes of drug discontinuation or switching between NOACs neither treatment adherence between annual prescriptions.

The actual lack of linkage with the national outcome databases prevented us from collecting data on effectiveness and safety of NOACS in Italian population. These critical issues will be the aim of future analyses.

6. Conclusions

In conclusion, we presented the data of AIFA monitoring registry, including about one-third of Italian patients with AF, treated since 2013 with NOACs. To the best of our knowledge, this is the largest real-world study ever published on NOACs.

These data have added value to be representative of the entire NOACs Italian prescription providing the real picture of NOACs prescription. In comparison with previous observations and pivotal trials, our population consisted of very elderly patients, at high risk of events. Since the specific characteristics of our patients, further analyses are needed to analyze the effectiveness and safety of NOACs in our country.

CRediT authorship contribution statement

P.P. Olimpieri: Conceptualization, Methodology, Formal analysis, Visualization, Writing - original draft, Writing - review & editing. **A. Di Lenarda:** Writing - review & editing, Conceptualization. **F. Mammarella:** Conceptualization, Writing - original draft, Writing - review & editing. **L. Gozzo:** Conceptualization, Writing - original draft, Writing - review & editing. **A. Cirilli:** Writing - original draft, Writing - review & editing. **M. Cuomo:** Formal analysis, Methodology. **M.M. Gulizia:** Writing - review & editing. **F. Colivicchi:** Writing - review & editing. **G. Murri:** Project administration, Supervision, Conceptualization. **D. Gabrielli:** Supervision, Writing - review & editing. **F. Trotta:** Conceptualization, Supervision, Methodology.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2019.100465.

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