Original article

Anticoagulation in atrial fibrillation. A large real-world update

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ABSTRACT

Introduction: In a large nationwide administrative database including ~35 % of Italian population, we analyzed the impact of oral anticoagulant treatment (OAT) in patients with a hospital diagnosis of non-valvular atrial fibrillation (NVAF).

Methods and results: Of 170404 OAT-naïve patients (mean age 78.7 years; 49.4 % women), only 61.1 % were prescribed direct oral anticoagulants, DOACs, or vitamin-K antagonists, VKAs; 14.2 % were given aspirin (ASA), and 24.8 % no anti-thrombotic drugs (No Tx). We compared ischemic stroke (IS), IS and systemic embolism (IS/SE), intracranial hemorrhage (ICH), major bleeding (MB), major gastro-intestinal bleeding, all-cause deaths and the composite outcome, across four propensity-score matched treatment cohorts with >15400 patients each.

Over 2.9±1.5 years, the incidence of IS and IS/SE was slightly less with VKAs than with DOACs (1.62 and 1.84 vs 1.81 and 1.99 events.100 person-years; HR=0.85, 95%CI=0.76-0.95 and HR=0.87, 95%CI=0.78-0.97). This difference disappeared in a sensitivity analysis which excluded those patients treated with low-dose of apixaban, edoxaban, or rivaroxaban (41.7% of DOACs cohort). Compared with DOACs, VKAs were associated with greater incidence of ICH (1.09 vs 0.81; HR=1.38, 95%CI=1.17-1.62), MB (3.78 vs 3.31; HR=1.14, 95%CI=1.02-1.28), all-cause mortality (9.66 vs 10.10; HR=1.07, 95%CI=1.02-1.11), and composite outcome (13.72 vs 13.32; HR=1.04, 95%CI=1.01-1.08). IS, IS/SE, and mortality were more frequent with ASA or No Tx than with VKAs or DOACs (p<0.001 for all comparisons).

Conclusions: Beyond confirming the association with a better net clinical benefit of DOACs over VKAs, our findings substantiate the large proportion of NVAF patients still inappropriately anticoagulated, thereby reinforcing the need for educational programs.

1. Introduction

Oral anticoagulant treatment (OAT) is strongly recommended for the prevention of ischemic stroke or systemic embolism in patients with non-valvular atrial fibrillation (NVAF) and additive risk factors for cardio-embolic events. Evidence from randomized controlled trials (RCTs) [1] and observational studies consistently demonstrated a superior net clinical benefit of direct oral anticoagulants (DOACs) over

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Abbreviations: ASA, aspirin; DOACs, direct oral anticoagulants; ICH, intracranial hemorrhage; IS, ischemic stroke; MB, major bleeding; MGIB, major gastro-intestinal bleeding; No Tx, no antithrombotics; NVAF, non-valvular atrial fibrillation; SE, systemic embolism; VKAs, vitamin K antagonists.

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vitamin K antagonists (VKAs) [2,3] although such a superiority may differ among DOACs [4,5]. Thus, current guidelines recommend that DOACs should be preferred over VKAs for patients with NVAF at risk of stroke [6–10]. However, despite international recommendations and increasing use of DOACs, under-prescription of OAT in NVAF is still common particularly in older persons, approaching 50% in several clinical settings [11–15]. Beyond clinical inertia, advanced age, physical frailty and comorbidities, a perceived high risk of age- and fall-related bleedings, and uncertain benefit in front of reduced life-expectancy, are frequent reasons for not prescribing OAT [12,15–17]. As a consequence, a large proportion of older persons with NVAF are currently left untreated or inappropriately prescribed antiplatelets, mainly aspirin (ASA) [11,14,15], following the mistaken belief of a lower bleeding risk compared to OAT. Also, most real-world studies that compared DOACs with VKAs did not address the whole spectrum of NVAF patients and left unexplored the segment of those untreated, because the index event determining the eligibility for inclusion in those analyses was initiation of OAT, rather than the diagnosis of NVAF [2–4].

We therefore hypothesized that adopting "diagnosis of NVAF" rather than "prescription of OAT in NVAF" as a search field for inclusion in the analysis, might provide a more informative snapshot of current clinical practice in the real world. By focusing the study on the characteristics of NVAF patients according to their on- or off-treatment destination, our aim was to investigate the background of prescription decision-making and the associated outcomes. We also hypothesized that investigating the effectiveness and safety of DOACs vs. ASA in our real-world population, might extend our knowledge in this area, beyond that provided by RCTs [18].

Thus, to assess the current practice and its clinical implications more than ten years after DOACs introduction into the Italian pharmacopoeia, we evaluated the comparative risks of ischemic stroke (IS), IS and systemic embolism (IS/SE), intracranial hemorrhage (ICH), major bleeding (MB), major gastro-intestinal bleeding (GIB), and all-cause mortality in patients who, after a hospital-based diagnosis of NVAF, were prescribed with: 1) DOACs (dabigatran, rivaroxaban, apixaban, or edoxaban); 2) VKAs; 3) ASA; or 4) no antithrombotic therapy (No Tx).

2. Methods

2.1. Data source

Data were extracted from three administrative databases of a sample of Italian Local Health Units (LHUs) covering approximately 35 % of the Italian general population across 9 regions. Such databases track all healthcare resources reimbursed by the Italian National Health Service (INHS) and provide information on: (i) demographics (age, sex), and vital status (accounting for all-cause mortality); (ii) drugs prescriptions, such as brand name, Anatomical-Therapeutic Chemical (ATC) code, marketing authorizations code, number of packages, number of units per package, and prescription date; this database includes the community pharmaceutical flow as well as the direct pharmaceutical distribution flow, which allows also to identify medicines dispensed by INHS hospitals for outpatients use; (iii) hospitalizations, including discharge diagnoses coded with the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), Diagnosis Related Group (DRG) and DRG-related charge. For the current analysis, LHUs were selected by geographical distribution, completeness of the databases and high-quality of the collected data. Accordingly, information represented the practice of public and private hospitals operating within the national health service. To comply with privacy recommendations of European Union Data Privacy Regulation 2016/679 ("GDPR") and Italian laws (D. lgs. n. 196/2003, as amended by D.lgs. n. 101/2018), each individual patient's unique identifier (fiscal code) was immediately converted by a computerized routine into an anonymous code, which allowed electronic linkage among databases. All results of the analyses were produced as aggregated summaries, which could not be connected, either directly or indirectly, to individual subjects. Such a routine and the whole study protocol were approved by the Ethics Committees of the LHUs that adhered to the study.

2.2. Study design

This observational study consisted of a retrospective analysis of patients with a first hospital discharge diagnosis of NVAF (ICD-9-CM code: 427.31) between January 2015 and September 2018 (inclusion period), which was taken to represent the index event. We excluded patients with a prescription of OAT or antiplatelets during the five years preceding the index event. Patients included in the analysis were distributed into four mutually exclusive cohorts, based on therapy prescribed at discharge: i) DOACs cohort (dabigatran, ATC code: B01AE07; rivaroxaban, ATC code: B01AF01; apixaban, ATC code: B01AF02; edoxaban, ATC code: B01AF03); ii) VKAs cohort (warfarin, ATC code: B01AA03; acenocoumarol, ATC code: B01AA07); iii) ASA cohort (ATC code: B01AC06); iv) no prescription of any of such antithrombotic agents (No Tx cohort). In the first three cohorts, first drug prescription was taken to represent the index date for initiation of follow-up, whereas in the fourth one the index date was represented by NVAF diagnosis.

In order to better describe our population and to exclude previous episodes of AF, all patients had at least 5 years of data available before the index event for backward characterization and, in the absence of any clinical outcome, at least a 12-month follow-up. In addition to prior prescription of OAT or antiplatelets, exclusion criteria were rheumatic mitral valve stenosis or presence of mechanical prosthetic heart valves during the characterization period. Patients who switched among anticoagulants during the follow-up were included in the descriptive analysis but excluded from analysis of outcomes.

2.3. Study variables

Demographics were collected at the index date, and clinical variables were assessed during the pre-index period. The CHA_2DS_2-VASc score [19] was reported as mean±standard deviation (SD); patients were also grouped according to predetermined CHA_2DS_2-VASc score cutoffs of 1-2, 3 and >3. The HAS-BLED score [20], in which – due to the administrative nature of our database - H stands for "hypertension" rather than "uncontrolled hypertension", was also reported as mean ±SD. Other therapies recorded over the same period included non-steroidal anti-inflammatory drugs (NSAIDs) (ATC code: M01A), P2Y12 inhibitors (ATC codes: B01AC04, B01AC22, B01AC24), anti-hypertensives (ATC codes: C02, C03, C07, C08, C09), lipid-lowering drugs (ATC code: C10), treatments for oncologic disease (ATC code: L01 or DRG 410 or procedural codes 99.25, 99.28, 99.29), antipsychotics (ATC code: N05), antidepressants (ATC code: N06A), and acetyl-cholinesterase inhibitors used for the treatment of dementia (ATC codes: N06D, N07A). The Charlson Comorbidity Index (CCI) [21] was assessed by the clinical variables available over the 5-year characterization period. Previous hospitalizations and drugs prescribed were collected, respectively, over 5 years and 3 months prior to the index date.

2.4. Statistical analysis

Continuous and categorical variables were reported, respectively, as mean±SD, and as numbers and percentages. Since the observational nature of the study may result in groups differences for demographic and clinical variables, propensity score matching (PSM) was used to balance both baseline characteristics and number of patients across the above defined four cohorts, in order to minimize the effects of selection bias. Patients were matched by quintiles of propensity score calculated using a logistic regression model that included all baseline characteristics (in particular, age, sex, CHA_2DS_2-VASc and HAS-BLED scores, CCI, and number of prior hospitalizations and drugs), and, to obtain equinumeric

cohorts, a 1:1:1:1 algorithm was used to match subjects in each quintile of the 4 treatment cohorts (DOACs, VKAs, ASA, No Tx). Model calibration and discrimination were assessed using respectively the Hosmer-Lemeshow test and the Receiver Operating Characteristic (ROC) analysis. Hosmer-Lemeshow test was not significant, while ROC value was 73.5. Pre- and post-PSM cohorts were compared by using the standardized mean difference (SMD). A SMD <0.10 in the post-PSM comparison was taken to indicate that the cohorts were well balanced.

Effectiveness outcomes included IS, the combination IS/SE, and all-cause mortality, whereas safety outcomes included ICH, MB, and GIB, coded as reported in Supplementary Table 1. Of note, our definition of "major" bleeding was based on hospital discharge diagnosis. Events were classified as fatal when death occurred within 30 days from hospitalization discharge. Moreover, a composite of effectiveness and safety outcomes was taken to assess the net clinical benefit. Patients were censored after a first recorded event; however, all outcomes were analyzed separately, meaning that while patients might have experienced more than a single outcome (e.g., a stroke and a major bleed), repeated events (i.e., a second stroke after a first one) were not included in the analysis. Thus, a patient with both a stroke and a major bleed was included in the stroke analysis up to the time of first stroke, and in the major bleed analysis up to the time of first major bleed. The time-to-event was calculated based on the date of first prescription and the date of hospital admission or of death, as applicable.

Crude incidence rates were expressed as events.100 person-years. Statistical analysis of treatment outcomes was conducted using multivariate Cox proportional hazard models to estimate Hazard Ratios (HR) with 95 % confidence intervals (95 %CI) after PSM. The proportional hazards assumption was tested using Schoenfeld scaled and unscaled residuals. Statistical significance was accepted for p values <0.05. All analyses were performed using STATA SE version 12.0.

3. Results

During the inclusion period, 170404 individuals had a hospital discharge diagnosis of NVAF (mean age 78.7 years; 49.4% women). Of these, 24231 were prescribed DOACs (14.2%), 79852 VKAs (46.9%), 24133 ASA (14.3%), and 42188 (24.8%) No Tx (Table 1). The vast majority of OAT patients were prescribed VKAs rather than DOACs during the first enrollment year, while this proportion was inverted from the second year (Fig. 1).

Patients receiving DOACs and VKAs were more often discharged from Cardiology than from Internal Medicine, Geriatrics and Neurology wards.

Those who were prescribed ASA were older and had a lower proportion of NVAF as the main diagnosis and a higher HAS-BLED score (Table 1). Patients receiving DOACs had more prior hospitalizations and

assumed a larger number of drugs per day. Compared with the other groups, the highest and the lowest proportion of patients with CHA_2DS_2-VASc >3 were those receiving ASA (64%) and No Tx (42.3%), respectively. These latter patients also had the lowest HAS-BLED score, as well as the lowest prevalence of hypertension, diabetes and prescription of cardiovascular drugs (Table 1, Supplementary Tables 2 and 3).

After PSM, all the SMDs became non-significant, confirming that the matching procedure had successfully balanced the four cohorts, each of about 15400 patients (Table 2, Supplementary Table 4). Also, in the characterization period, the prevalence of a previous hospitalization for an acute coronary syndrome was low in all cohorts (DOACs: 0.26%; VKAs: 0.21%; ASA: 0.30%; No Tx: 0.16%).

3.1. Clinical outcomes

Fig. 2 reports the incidence and the propensity-weighted Cox HRs with 95%CIs for each clinical event observed in the follow-up (length-mean: 2.9±1.5 years; median, 25th-75th percentile: 3.1, 1.6-4.4 years) of the PSM cohorts receiving VKAs, ASA and No Tx, with DOACs-treated cohort assumed as the reference. Overall and fatal clinical events, including their numbers, person-years of follow-up and incidence rate for 100.person-years, are reported in Supplementary Tables 5 and 6. The incidence of IS was highest in ASA and No Tx groups, this latter showing also the highest rates of fatal IS and IS/SE (Fig. 2 and Supplementary Tables 5 and 6). The incidence of IS and of IS/SE was slightly lower in VKAs- than in DOACs-treated patients (Fig. 2 and Supplementary Table 5). Conversely, the incidence of ICH was lowest with DOACs compared to VKAs, ASA and No Tx groups, and that of MB followed a similar pattern (Fig. 2 and Supplementary Table 5). Rates of major GIB were similar across the four treatment cohorts. All-cause mortality was highest in No Tx and ASA groups, intermediate in VKAs- and lowest in DOACs-treated groups (Fig. 2 and Supplementary Table 5). All-cause mortality was significantly lower in DOACs than in VKAs group (p=0.004).

The net clinical benefit expressed by the combination of effectiveness and safety outcomes was significantly greater with DOACs than with VKAs, ASA and No Tx (Table 3).

3.2. Sensitivity analysis

To further analyze the superiority of VKAs over DOACs in preventing IS and IS/SE, we performed a sensitivity analysis with exclusion of low-dose DOACs, which were prescribed to as many as 10113 (41.7%) of the overall DOACs sample and to 6883 (44.7%) of the post-PSM cohort, respectively. Given the administrative nature of the dataset, we could not ascertain how many of these low doses were appropriate. Since dabigatran 110 mg b.i.d. cannot be regarded as a potentially

Table 1
Baseline demographic and clinical variables by treatment prescription.

	DOACs (N=24231)	VKAs (N=79852)	Aspirin (N=24133)	No Tx (N=42188)	SMD
Age (mean, SD)	77.7 (10.3)	78.2 (9.3)	81.0 (10.7)	78.7 (13.5)	0.149
Women (n, %)	12127 (50.0)	36503 (45.7)	12786 (53.0)	22739 (53.9)	0.074
CHA_2DS_2-VASc (mean, SD)**	3.90 (1.47)	3.78 (1.30)	3.87 (1.33)	3.19 (1.56)	0.191
CHA_2DS_2-VASc <3 (n, %)**	3918 (16.2)	11867 (14.9)	3397 (14.1)	12876 (30.5)	0.146
CHA_2DS_2-VASc =3 (n, %)**	5280 (21.8)	19336 (24.2)	5284 (21.9)	11480 (27.2)	0.062
CHA_2DS_2-VASc >3 (n, %)**	15033 (62.0)	48649 (60.9)	15452 (64.0)	17832 (42.3)	0.156
HAS-BLED (mean, SD)**	2.63 (1.00)	2.38 (0.89)	2.73 (0.88)	2.00 (1.17)	0.315
CCI (mean, SD)***	1.61 (1.52)	1.49 (1.51)	1.69 (1.60)	1.45 (1.78)	0.076
AF as main diagnosis (n, %)	8140 (33.6)	28627 (35.9)	4285 (17.8)	9766 (23.1)	0.216
Prior Hospitalizations* (mean, SD)	0.55 (0.71)	0.24 (0.55)	0.23 (0.56)	0.14 (0.45)	0.558
Prior Drugs* (mean, SD)	6.06 (3.69)	5.63 (3.36)	5.56 (3.43)	3.39 (3.60)	0.333
DOACs/VKAs switch (n, %)	2876 (11.9)	25626 (32.1)	3783 (15.7)	0 (0.0)	-

Note. CCI: Charlson Comorbidity Index; No Tx: no anticoagulants/aspirin
  * over the last 3 months,
  ** 12 months,
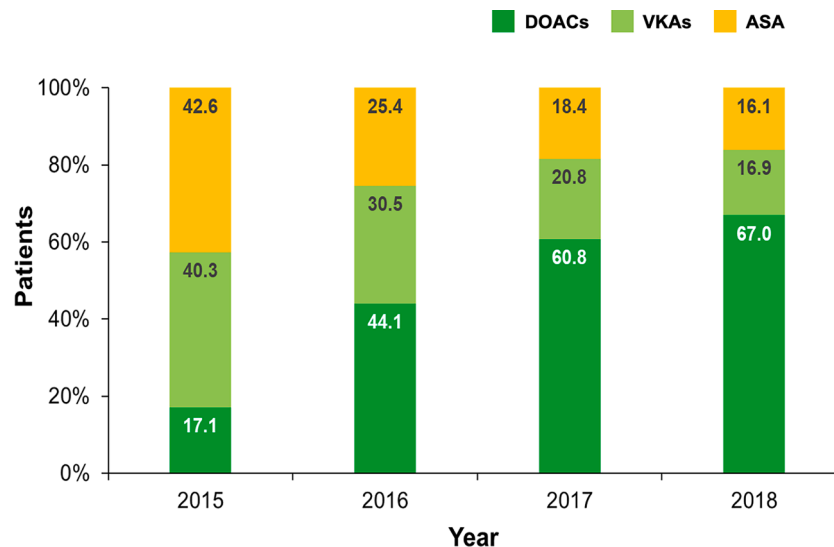 *** 5 years prior to index date.

Fig. 1. Proportions of antithrombotics prescribed over the enrollment years. (ASA: aspirin; DOACs: direct oral anticoagulants; VKAs: vitamin-K antagonists).

Table 2
Demographic and clinical variables in propensity score matched population, by treatment prescription.

	DOACs (N=15414)	VKAs (N=15415)	ASA (N=15424)	No Tx (N=15424)	SMD
Age (mean, SD)	78.9 (10.0)	78.6 (9.2)	79.0 (11.4)	79.0 (12.2)	0.016
Women (n, %)	7920 (51.4)	7744 (50.2)	7997 (51.8)	7957 (51.6)	0.012
CHA_2DS_2-VASc (mean, SD)**	3.75 (1.38)	3.71 (1.34)	3.77 (1.41)	3.77 (1.52)	0.018
CHA_2DS_2-VASc <3 (n, %)**	2595 (16.8)	2552 (16.6)	2756 (17.9)	2824 (18.3)	0.025
CHA_2DS_2-VASc =3 (n, %)**	3699 (24.0)	3836 (24.9)	3304 (21.4)	3427 (22.2)	0.041
CHA_2DS_2-VASc >3 (n, %)**	9120 (59.2)	9027 (58.6)	9364 (60.7)	9173 (59.5)	0.017
HAS-BLED (mean, SD)**	2.57 (0.96)	2.54 (1.00)	2.59 (0.90)	2.56 (1.14)	0.020
CCI (mean, SD)***	1.59 (1.59)	1.57 (1.56)	1.62 (1.53)	1.59 (1.66)	0.010
Prior Hospitalizations* (mean, SD)	0.31 (0.56)	0.31 (0.64)	0.31 (0.65)	0.30 (0.64)	0.012
Prior Drugs* (mean, SD)	5.48 (3.43)	5.43 (3.46)	5.53 (3.50)	5.47 (3.89)	0.011

Abbreviations as in Table 1

inappropriate dose reduction [22], the sensitivity analysis compared the risk of events between VKAs-treated patients and those treated with any dose of dabigatran or full-dose inhibitors of activated factor X (anti-Xa). In this analysis, the effectiveness of VKAs and DOACs was non-significantly different, whereas DOACs were confirmed to be consistently superior to VKAs for most safety outcomes and for the net clinical benefit (Table 4).

Finally, we focused on the high rate of MB (3.56 events.100-person years) in the No Tx patients: a finding that, at first glance, we deemed difficult to be explained. At detailed analysis, we found that as many as 22995 (54.5%) of the whole cohort and 9453 (61.3%) of the post-PSM cohort of these "supposedly" No Tx patients, had been prescribed with off-label low-molecular weight heparins (LMWHs) for a mean of 66±165 days (median, 25th-75th percentile: 20 days, 1-60 days). Importantly, pulmonary artery embolism and deep vein thrombosis had been responsible of a hospital admission in the preceding 12 months in only 12 cases (0.08%).

4. Discussion

To the best of our knowledge, this is the largest available outcome-based study conducted in patients discharged from hospital with a diagnosis of NVAF and analyzed by prescription of DOACs, VKAs, ASA, or no Tx. Our principal findings are as follows: (i) only 61% of patients with a hospital diagnosis of NVAF were prescribed OAT, whereas the remaining 39% were prescribed ASA or No Tx (neither OAT nor ASA); (ii) prescription of DOACs steadily increased over the study period and became greater than prescription of VKAs from the second enrollment

year; (iii) the prescription of low-dose DOACs was much more frequent than that reported in RCTs; (iv) we confirmed, in the overall sample, the association with a better net clinical benefit of DOACs over VKAs; this was even larger when only patients receiving full-dose DOACs were selected for analysis; and (v) compared with OAT patients, those receiving ASA or a No Tx regimen (that was represented by LMWH in more than 50% of the whole sample and in almost 2/3 of the post-PSM cohort) had more IS/SE, more ICH and MB, and a higher all-cause mortality.

The demographic and clinical variables of our study population were similar to recent cohort studies [3]. However, by including patients with a hospital diagnosis of NVAF irrespective of OAT prescription, compared with previous studies based on nationwide registries or healthcare and administrative datasets [23], our study population was older, with a larger proportion of women, and with higher mean CHA_2DS_2-VASc score, number of comorbidities and of concomitant chronic drug therapies.

In our study, only 61% of patients with NVAF were prescribed OAT, a proportion consistent with recent general population studies that reported even lower rates [12,14,15]. Overall, we found that more than a half of OAT patients received VKAs rather than DOACs, but, as in other experiences [24], this difference originated by a much larger prescription of VKAs only during the first enrollment period. Notably, this resulted in a slightly shorter mean follow-up in the DOACs compared with the VKAs cohort (2.4 vs. 3.2 years, respectively).

In accordance with previous studies, we confirmed a greater net clinical benefit of DOACs over VKAs, mainly due to lower rates of ICH, MB events [2,3,25], and all-cause mortality. In the PSM-adjusted
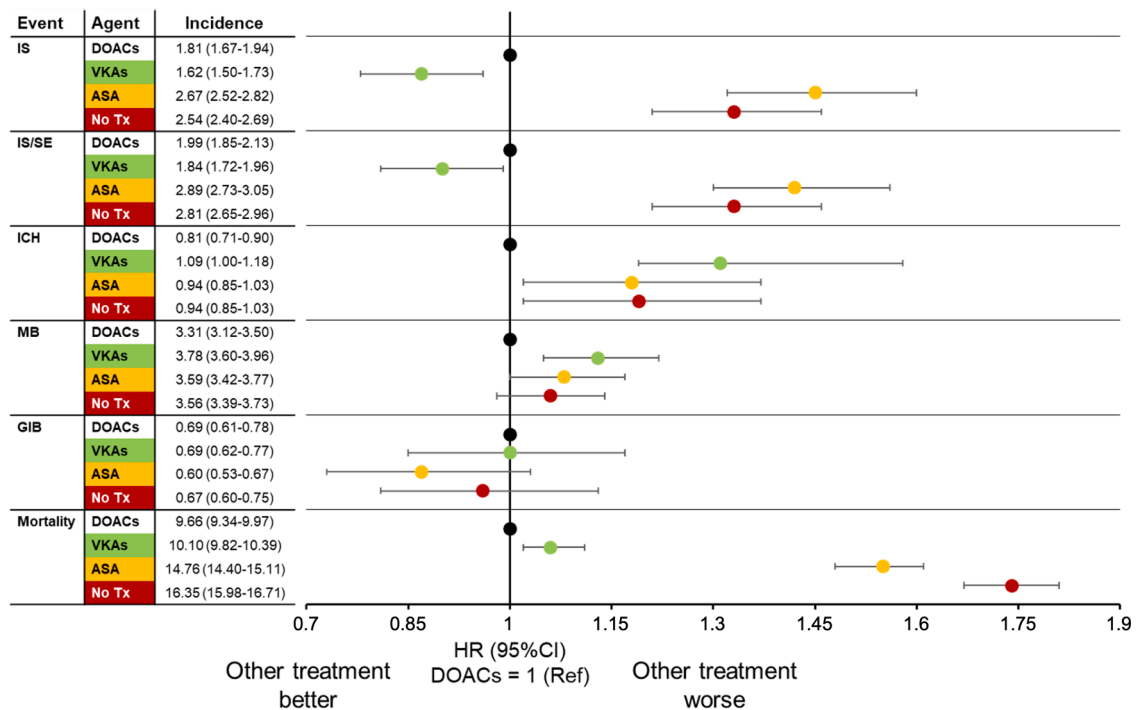
Fig. 2. Incidence of events (n.100 person-years) by anti-thrombotic therapy in NVAF patients. Hazard ratios and 95% confidence intervals (HR; 95%CI) derived from multivariate Cox regression analysis assuming DOACs treatment as the reference one. (GIB: major gastro-intestinal bleeding; ICH: intracranial hemorrhage; IS: ischemic stroke; MB: major bleeding; SE: systemic embolism).

Table 3

Incidence of effectiveness and safety composite outcomes, with hazard ratios (HR) and related 95% confidence intervals (95%CI), by prescribed treatment.

Treatment	Incidence (95%CI)[a]	HR (95%CI)	p value
DOACs	13.32 (12.94 - 13.70)	Reference	-
VKAs	13.72 (13.38 - 14.06)	1.04 (1.01-1.08)	0.027
ASA	18.29 (17.89 - 18.70)	1.39 (1.34-1.44)	<0.001
No Tx	19.67 (19.26 - 20.08)	1.50 (1.45-1.55)	<0.001
P value	<0.001	/	/

[a] Incidence: events for 100 person-years

Table 4

Hazard ratios (HR) and 95% confidence intervals (95%CI) for clinical events in VKAs-treated vs. full-dose DOACs-treated patients (reference).

Events*	All events		Fatal events	
	HR (95%CI)	p value	HR (95%CI)	p value
IS	0.94 (0.85-1.05)	0.269	1.13 (0.86-1.48)	0.390
IS/SE	1.00 (0.90-1.10)	0.943	1.21 (0.93-1.58)	0.153
ICH	1.35 (1.17-1.57)	<0.001	1.91 (1.36-2.69)	<0.001
MB	1.28 (1.19-1.39)	<0.001	1.95 (1.48-2.56)	<0.001
Major GI bleeding	1.19 (1.00-1.41)	0.046	1.78 (0.87-3.65)	0.117
All-cause death	1.30 (1.23-1.37)	<0.001	/	/
Composite outcome	1.22 (1.17- 1.27)	<0.001	/	/

Note. IS: ischemic stroke; SE: systemic emboli; ICH: intra-cranial hemorrhage; MB: major bleeding; GI: gastrointestinal

* Pooled dabigatran 150 or 110 mg b.i.d. and only full-dose anti-Xa

analysis, we found a marginal but significantly greater effectiveness of VKAs over DOACs in reducing IS and IS/SE. However, more than 40% of patients in either the overall sample or the post-PSM cohort received DOACs at low doses, which might have been inappropriately reduced in a large proportion of them. These figures are consistent with those reported in previous real-world studies and meta-analyses, which found that underdosing was associated with reduced efficacy of anti-Xa agents [4,5,26–28]. As in many other observational studies based on administrative data, we could not identify patients with inappropriately low doses of anti-Xa inhibitors. In a further sensitivity analysis with exclusion of patients treated at a reduced dosage of anti-Xa inhibitors, the incidence of IS and IS/SE became similar in VKAs- and DOACs-treated cohorts. This indirectly confirmed the hypothesis that the slightly superior effectiveness of VKAs over DOACs that we had found in the PSM population as a whole, might be attributed to a large proportion of inappropriately reduced anti-Xa doses. Following this approach, the net clinical benefit of DOACs over VKAs became even larger than previously observed with any DOACs dose and, consistently with previous studies, this result was largely driven by a reduced all-cause mortality with DOACs [2,4,25].

Compared with DOACs-treated patients, those receiving ASA had higher rates of IS, IS/SE, ICH, MB, and all-cause mortality. These findings, which are consistent with those of the AVERROES trial [18], should definitely discourage the prescription of ASA to NVAF patients, as clearly recommended in international guidelines [6,7].

The high rate of MB was an unexpected finding in our No Tx patients. Indeed, such bleeding rates were similar to those we observed with ASA or VKAs, and higher than those with DOACs. Such a high rate was not accounted for by a higher prevalence of cancer or of use of drugs associated with an increased hemorrhagic risk, whereas we found that it was associated with an off-label prescription of LMWHs to almost two thirds of the No Tx patients. Of note, although LMWHs were associated with a higher risk of MB, the incidence of new fatal events was similar to that observed among "truly" untreated subjects.

All-cause mortality was higher in both ASA-treated and No Tx patients than in those taking OAT, even after PSM adjustment. In both No Tx and ASA-treated cohorts, we did not find a worse overall health status or a socially disadvantaged profile, and prescription prevalence of drugs for dementia was also similar. In previous studies, the prescription of

OAT was relatively independent of general health status or presence of frailty [13–15], with about 25% of patients not prescribed OAT in the absence of any plausible reason. In our study, we were unable to identify plausible reasons for not prescribing OAT to such a huge proportion of patients and to identify clinical variables accounting for exceedingly high mortality rates in the No Tx cohort. Although we cannot exclude the impact of some clinical inertia, OAT might have not been prescribed, at least in some patients, because of the clinical perception of poor general health and/or reduced life expectancy that, though not captured by variables available in an administrative database, might have led to higher all-cause mortality [29].

4.1. Study limitations and strengths

Some limitations of our study should be acknowledged. First, strict adherence to clinical profile required by the Italian regulatory authority might have contributed, particularly during the first study period, to limit the use of DOACs compared to other European Countries. Second, the impact of some unmeasured confounders, including relevant clinical variables and selective prescribing, cannot be excluded despite PSM. Third, we were unable to get information either on time in therapeutic range in VKAs users, or on adherence/persistency of OAT use, and we lacked fundamental laboratory and anthropometric measures for assessing the appropriateness of low doses of anti-Xa inhibitors. Moreover, in sensitivity analysis, we compared the effectiveness and the safety of DOACs vs. VKAs after having excluded those patients who were prescribed with low doses of anti-Xa inhibitors. This behavior could have determined the evaluation of a healthier population and the bias of the results. Underdosing of DOACs is, however, more frequently observed in Italy than in other European countries. Fourth, patients included in the study had a hospital-based diagnosis of NVAF, implying that those treated in the primary care setting – with potentially less compromised general health status – were not represented. Fifth, our data apply to a predominantly Caucasian European population, with limited generalizability to different ethnic groups. Sixth, the identification of endpoints necessarily relied on ICD-9-CM codes available from hospital discharge and on death records, with possible implications on the accuracy of findings, particularly regarding cardiovascular death, which were therefore deliberately excluded from outcomes. Seventh, as in the vast majority of observational, retrospective studies, multivariable adjustment was done with covariates scored at baseline only. Eight, chronic kidney disease (CKD) could not be evaluated in our population; only the most severe cases of the condition, in particular, those associated with hospital admission, usually figure in an administrative database, possibly leading to underestimate the real disease prevalence. However, the good clinical balance among cohorts after PSM should exclude a CKD-related different distribution of OAT. Finally, we only focused on OAT and non-OAT use, but we recognize the need for a more holistic or integrated care approach to managing these clinical complex NVAF patients [7,30].

Despite these limitations, our study has some strengths to be highlighted. In particular, since in our country access to health care is universal, electronic patient records are available for the whole population, without any selection criteria. Thus, records can be easily and reliably linked with each other, due to the presence of a unique patient's identifier and the validity and accuracy of the data stored in these records have repeatedly been assessed [31]. Therefore, this study depicts a reliable scenario of real-world treatment of NVAF in Italy, including the large proportion of patients who are not prescribed guideline-recommended OAT.

5. Conclusions

In conclusion, this nationwide, real-world Italian study shows that only about 60% of hospital-discharged NVAF patients are prescribed with OAT, with high proportions treated with VKAs or potentially inappropriate low doses of DOACs. Our findings confirm, in a huge population, that DOACs, when compared with VKAs, are associated with a lower incidence of ICH and MB, a lower all-cause mortality and a better net clinical benefit. Compared with OAT-treated patients, those receiving aspirin and those left without anti-thrombotic agents had higher risk of adverse clinical outcomes and mortality.

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Declaration of generative AI and AI-assisted technologies in the writing process

Nothing to disclose.

Data availability statement

The data underlying this article cannot be shared publicly because, even if derived from procedures generating anonymous codes and aggregated summaries, they were obtained using personal information contained in administrative databases belonging to the Local Health Units which participated to the project.

Declaration of Competing Interest

SF: speaker for BMS/Pfizer, Bruno Farmaceutici, Daiichi-Sankyo, Menarini Group; research grants from Menarini Group. GYHL: Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Anthos. GYHL is co-principal investigator of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 899871. NM: Consultant and speaker for BMS/Pfizer, Bayer, Daiichi-Sankyo. The other Authors declare they have no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2023.10.010.

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