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Direct oral anticoagulants vs non-vitamin K antagonist in atrial fibrillation: A prospective, propensity score adjusted cohort study

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1. Introduction

Oral anticoagulants directly inhibiting Factor IIa o Factor Xa (DOAC) have been marketed in Italy for the prevention of cardiac embolism in patients affected by non-valvular atrial fibrillation (NVAF) since 2013.

Several randomized controlled trials (RCTs) [1–4] and meta-analyses [5–10] have shown that DOAC are: a) at least non-inferior to vitamin K antagonist oral anticoagulants (VKA); b) in some cases more effective regarding the occurrence of stroke and mortality; c) always safer regarding the risk of intracranial hemorrhage (ICH).

However, some concerns were raised about the generalizability of these studies, due to the differences between patients included in these RCTs and those observed in clinical practice.

In fact, NVAF patients are often older, sicker, and carrying a bigger thrombotic and haemorrhagic risk than those included in most of the RCTs.

Recently, several observational studies have been performed to assess long-term effectiveness and safety of DOAC. Despite some clinical differences among populations involved in these studies and those involved in the RCTs, the efficacy and safety of these drugs were confirmed [11–16].

Heterogeneity among observational studies regarded design, i.e. registry or record linkage, prospective or retrospective studies, or clinical characteristics, i.e. naïve or experienced patients.

Besides, several studies did not provide enough information about the quality of VKA treatment, expressed as Time in Therapeutic Range (TTR). Moreover, some studies reported average TTR values ranging from 38% to 57% [17,18], which represent figures that have been recognized as associated with a 2.6-fold higher risk of stroke/systemic

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embolism, 1.5-fold higher risk of major bleeding, and 2.4-fold higher risk of all-cause mortality [19].

Another concern was present, which regarded the quality of VKA treatment, as a suboptimal management of it could affect the magnitude of the clinical benefit provided by DOACs.

Thus, we performed a prospective, observational study, aimed at comparing the effectiveness and safety of DOAC and VKA in the healthcare system of the Emilia-Romagna (ER) Region, in which the use of oral anticoagulants follows a clinical governance program.

2. Materials and methods

2.1. Study design

This was a multicenter, prospective, non-randomized, comparative effectiveness observational study, by record-linkage of administrative healthcare datasets with clinical data gathered in the study centers. Seven anticoagulation clinics of the ER Region, a region of northern Italy with about 4.5 million of inhabitants, were involved. The study protocol was approved by the locals Ethics Committees, starting from October 2014.

2.2. Data sources

The clinical history of each patient and its follow up were obtained by using several data sources.

Demographic and clinical information at baseline was directly recorded at enrolment, in each center involved in the study.

These data were linked to three ER Regional Healthcare System databases, including drug prescription database, hospital discharge database and the database of residents.

The first database includes all drug prescriptions reimbursed by the National Health System, and provides information about purchase date, number of dosing units and type of drugs. Drugs are reported according to the Anatomical Therapeutic Chemical (ATC) classification.

The second includes data on all patients discharged from private and public hospitals of ER Region. Diagnoses are coded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM).

The third one provides information on vital status of all ER Region residents.

All record-linkage operations among databases were performed in accordance with the Italian law, making use of anonymized identification codes.

2.3. Study population

From the date of approval until January 2017, all outpatients with a diagnosis of NVAF referring to the study centers for anticoagulant treatment were eligible to participate. Only adult (> 18 years old) patients with a diagnosis of NVAF requiring anticoagulant treatment according to current international guidelines [20,21] were included. Patients who were naïve to any anticoagulant treatment and those who already assumed VKA or DOAC were considered eligible. All patients who met the inclusion criteria, and gave their written informed consent, were enrolled in the study.

At enrollment the following characteristics were recorded: age, gender and clinical risk factors for thromboembolic and hemorrhagic events, such as CH_2ADS_2-VASc and HAS-BLED scores [22,23]. A modified version of HAS-BLED (hereinafter “modified HAS-BLED”) was used, as the “Labile INR” item, which is necessary to calculate the HAS-BLED score, was not available for all patients.

2.4. DOACs and VKAs use

The present study considers only Apixaban, Dabigatran and Rivaroxaban, as they were the only DOACs in use in Italy at the time of study approval. Edoxaban was not considered as it was introduced in Italy after the start of the study.

Use of anticoagulants was identified with the ATC classification. In particular, ATC codes B01AA03 (Warfarin) B01AA07 (Acenocumarol) identified the use of VKAs, while ATC codes B01AF02 (Apixaban), B01AE07 (Dabigatran), B01AF01 (Rivaroxaban) and B01AF03 (Edoxaban) identified the use of DOACs.

In this study, the start of anticoagulant therapy was defined as the first prescription of VKA or DOAC after the enrollment. The duration of DOACs therapy was indirectly estimated by considering one day of therapy for each Rivaroxaban and one day for every two Apixaban or Dabigatran prescribed pills. Whereas, for VKAs, the duration was obtained by considering one day of therapy for any amount of pill prescribed, which was estimated from the assessment of individual average prescription frequency.

2.4.1. Previous DOACs or VKAs use

Patients were classified into three categories, with respect to previous use of DOACs or VKAs:

a) VKA experienced, if they were on VKAs therapy for > 90 days in the 180 days before enrollment;
b) DOAC experienced, if they were on DOACs therapy for > 90 days in the 180 days before enrollment;
c) Naïve patients, in all the remaining cases.

2.5. Study outcomes

Primary outcomes of the study were:

a) a primary effectiveness outcome, corresponding to stroke or peripheral arterial embolism events.
b) a primary safety outcome, defined as bleeding in critical sites such as intracranial, spinal, gastrointestinal or intraocular bleeding, or any bleeding resulting in hospital admission.

Secondary outcomes of the study were:

a) a secondary safety outcome, corresponding to acute myocardial infarction (AMI) or other acute, subacute and chronic ischemic heart disease.
b) a composite outcome, corresponding to the occurrence of at least one of the previously listed primary and secondary outcomes.
c) all-causes mortality.

Outcome data concerning clinical events was gathered from the ER Region hospital discharge database. ICD-9-CM codes, which were used to identify the events of interest, are reported in Appendix I. The date of the event was defined as the day of hospital admission. With respect to mortality, data was gathered from the ER Region residents database.

2.6. Previous hospital admissions

Previous hospital admissions were assessed. For each patient, we evaluated the presence of pathological conditions, identified as possible

Table 1
Sample characteristics at baseline and concomitant drug use during follow-up, by cohort - Scenario 1.

			VKA (n = 1955)		DOACs (n = 2178)		Total (n = 4133)		P-value	
Demographic characteristics										
Age	Years	mean sd	77.40	8.22	75.43	8.88	76.36	8.63	0.0000	****
	≥ 80	n %	882	44.1%	737	33.8%	1619	39.2%	0.0000	****
Gender	M	n %	1123	57.4%	1168	53.6%	2291	55.4%	0.0137	*
Previous VKA or DOACs use										
Experienced	VKA	n %	1584	81.0%	167	7.7%	1751	42.4%	0.0000	****
	DOACs	n %	31	1.6%	9.8	43.1%	969	23.5%		
Naive		n %	340	17.4%	1073	49.3%	1413	34.2%		
CHA_2DS_2-VASc (+)										
Overall score	[0–9]	mean sd	3.69	1.30	3.38	1.33	3.51	1.33	0.0000	****
Congestive heart failure	Yes	n %	235	14.6%	230	10.5%	465	12.2%	0.0003	***
Hypertension	Yes	n %	1346	83.3%	1797	82.4%	3143	82.8%	0.9548	
Stroke / TIA / Thromboembolism	Yes	n %	225	13.9%	225	10.3%	450	11.9%	0.0010	**
Vascular disease	Yes	n %	301	18.6%	236	10.8%	537	14.1%	0.0000	****
Diabetes	Yes	n %	300	18.6%	426	19.5%	726	19.1%	0.3695	
Modified HAS-BLED (+)										
Overall score	[0–8]	mean sd	1.93	0.73	1.78	0.78	1.84	0.76	0.0000	****
Hypertension	Yes	n %	1159	71.8%	1430	65.5%	2589	68.2%	0.0004	***
Renal disease	Yes	n %	108	6.7%	82	3.8%	190	5.0%	0.0000	****
Liver disease	Yes	n %	16	1.0%	9	0.4%	25	0.7%	0.0316	*
Stroke	Yes	n %	188	11.6%	182	8.3%	370	9.7%	0.0011	**
Major bleeding	Yes	n %	60	3.7%	91	4.2%	151	4.0%	0.4366	
Medication	Yes	n %	91	5.6%	80	3.7%	171	4.5%	0.0049	**
Alcol or drugs	Yes	n %	4	0.2%	46	2.1%	50	1.3%	0.0000	****
Previous hospital admissions										
Congestive heart failure	Yes	n %	439	22.5%	341	15.7%	780	18.9%	0.0000	****
Peripheral vascular disease	Yes	n %	145	7.4%	98	4.5%	243	5.9%	0.0000	****
Hypertension, uncomplicated	Yes	n %	744	38.1%	843	38.7%	1587	38.4%	0.6684	
Hypertension, complicated	Yes	n %	335	17.1%	290	13.3%	625	15.1%	0.0006	***
Diabetes, uncomplicated	Yes	n %	234	12.0%	244	11.2%	478	11.6%	0.4418	
Diabetes, complicated	Yes	n %	47	2.4%	42	1.9%	89	2.2%	0.2928	
Liver disease	Yes	n %	49	2.5%	42	1.9%	91	2.2%	0.2061	
Alcol abuse	Yes	n %	13	0.7%	7	0.3%	20	0.5%	0.1120	
Drug abuse	Yes	n %	0	0.0%	0	0.0%	0	0.0%	–	
Other neurological disorders	Yes	n %	29	1.5%	53	2.4%	82	2.0%	0.0288	*
Myocardial infarction	Yes	n %	145	7.4%	127	5.8%	272	6.6%	0.0401	*
Cerebrovascular disease	Yes	n %	243	12.4%	382	17.5%	625	15.1%	0.0000	****
Renal disease	Yes	n %	167	8.5%	67	3.1%	234	5.7%	0.0000	****
Concomitant drugs										
Aspirin	Yes	n %	149	7.6%	134	6.2%	283	6.8%	0.0619	
Clopidogrel	Yes	n %	23	1.2%	14	0.6%	37	0.9%	0.0690	
ACE-inhibitors	Yes	n %	643	32.9%	633	29.1%	1276	30.9%	0.0078	**
Amiodarone	Yes	n %	151	7.7%	257	11.8%	408	9.9%	0.0000	****
Statins	Yes	n %	869	44.5%	882	40.5%	1751	42.4%	0.0102	*
Proton pump inhibitors	Yes	n %	697	35.7%	973	44.7%	1670	40.4%	0.0000	****
H_2-receptor antagonists	Yes	n %	39	2.0%	51	2.3%	90	2.2%	0.4458	
Beta-blockers	Yes	n %	1422	72.7%	1535	70.5%	2957	71.5%	0.1080	
Heparin	Yes	n %	6	0.3%	2	0.1%	8	0.2%	0.1163	

DOACs = Direct Oral Anticoagulants; VKA = Vitamin K Antagonists; sd = standard deviation; (+) = data was gathered for 1627 and 2174 patients, respectively.
* $p < .05$.
** $p < .01$.
*** $p < .001$.
**** $p < .0001$.

confounders, from previous hospital discharges. The Elixhauser Comorbidity and the Charlson Comorbidity Indexes were used to classify these conditions [24]. The list of them and their relative ICD-9-CM codes are reported in Appendix I. We only considered discharges occurred from 1-st January 2009 to the date of enrollment.

2.7. Concomitant drug use

Starting from 30 days after the date of enrolment until the end of follow-up, for each patient we evaluated whether they received any concomitant prescription of the following ten drug categories: aspirin (ATC codes N02BA01, B01AC06), clopidrogel (B01AC04), ACE-inhibitors (C09AA), amiodarone (C01BD01), statins (C10A), proton pump inhibitors (A02BC), H_2-receptor antagonists (A02BA), beta-blockers (C07) and heparin (B01AB01).

2.8. Statistical analysis

Characteristics of patients at enrolment were summarized by means of descriptive statistics. Continuous variables were expressed as means and standard deviations, while categorical variables as absolute and percentage frequencies. Comparisons were performed with t-test and chi-square test, respectively.

Two scenarios were considered. In both of them, patients were assigned to cohorts on the basis of the drug that was first prescribed after enrolment.

Table 2
Incidence outcome rates, by cohort - Scenario 1.

Outcome		VKA		DOACs		Total	
All patients (n = 4133)							
Effectiveness - primary	e e%p-y	25	1.14	22	0.81	47	0.96
Stroke	e e%p-y	16	0.73	21	0.77	37	0.75
Peripheral arterial embolism	e e%p-y	9	0.41	1	0.04	10	0.20
Safety - primary	e e%p-y	37	1.69	52	1.91	89	1.81
Intracranial hemorrhage	e e%p-y	10	0.46	18	0.66	28	0.57
Spinal hemorrhage	e e%p-y	–	–	1	0.04	1	0.02
Other major bleeding	e e%p-y	7	0.32	2	0.07	9	0.18
Gastrointestinal hemorrhage	e e%p-y	18	0.82	32	1.18	50	1.02
Intraocular hemorrhage	e e%p-y	2	0.09	–	–	2	0.04
Safety - secondary	e e%p-y	112	5.12	123	4.52	235	4.79
Acute myocardial infarction	e e%p-y	22	1.01	16	0.59	38	0.77
Other ischemic heart disease	e e%p-y	98	4.48	112	4.11	210	4.28
Composite outcome	e e%p-y	166	7.59	186	6.83	352	7.17
Death	e e%p-y	32	1.46	46	1.69	78	1.59
Only naive patients (n = 1413)							
Effectiveness - primary	e e%p-y	3	0.99	14	1.08	17	1.06
Stroke	e e%p-y	3	0.99	13	1.00	16	1.00
Peripheral arterial embolism	e e%p-y	–	–	1	0.08	1	0.06
Safety - primary	e e%p-y	5	1.65	23	1.77	28	1.75
Intracranial hemorrhage	e e%p-y	1	0.33	10	0.77	11	0.69
Spinal hemorrhage	e e%p-y	–	–	–	–	–	–
Other major bleeding	e e%p-y	2	0.66	2	0.15	4	0.25
Gastrointestinal hemorrhage	e e%p-y	2	0.66	12	0.92	14	0.87
Intraocular hemorrhage	e e%p-y	–	–	–	–	–	–
Safety - secondary	e e%p-y	31	10.24	72	5.54	103	6.43
Acute myocardial infarction	e e%p-y	7	2.31	8	0.62	15	0.94
Other ischemic heart disease	e e%p-y	27	8.92	66	5.08	93	5.80
Composite outcome	e e%p-y	37	12.22	102	7.85	139	8.68
Death	e e%p-y	5	1.65	20	1.54	25	1.56

DOACs = Direct Oral Anticoagulants; VKA = Vitamin K Antagonists; e = number of events; e%p-y = number of events per 100 person-years.

2.8.1. Scenario 1 – All DOACs vs VKAs

All DOACs were considered as a whole and the comparison was carried out between VKAs and DOACs cohorts.

2.8.2. Scenario 2 – Individual DOACs vs VKAs

DOACs were considered separately, resulting in three cohorts: Apixaban, Dabigatran, Rivaroxaban and the following comparisons were assessed:

a) Apixaban vs VKA;
b) Dabigatran vs VKA;
c) Rivaroxaban vs VKA.

2.8.3. Incidence rates

Crude incidence rates for the study outcomes, in the whole sample and stratified by cohort, were calculated as number of events per 100 person-years.

2.8.4. Time-to-event analysis

In order to compare risk of outcomes between cohorts, an *as-treated* analysis was performed. Statistical modeling was carried out in a competing risk setting, being every patient at risk of experiencing different outcomes. Hence, Fine & Gray proportional hazards models (FG) were used to assess the relationship between the study cohorts and the outcomes [25]. Results of FG models were reported as sub-distribution hazard ratios (HR) with 95% confidence intervals (95% CI).

Each patient was included in the study starting from the date of first VKAs or DOACs prescription after enrollment, until the occurrence of the first among the following events: any outcome event previously listed, death, therapy interruption and cohort switch (including all switches to Edoxaban).

Switches were defined as the change of anticoagulant treatment decided by the attending physician.

Due to the possibility of experiencing more than one outcome simultaneously, we carried out a separate analysis for each of them, every time considering the remaining outcomes as competing events. Patients that switched cohort or interrupted their therapy, as well as patients who were event-free at 31-st July 2017, were treated as censored observations.

In both scenarios, an "unadjusted" analysis was performed, by estimating sub-distribution hazard ratios by means of FG models and using cohort as the independent variable.

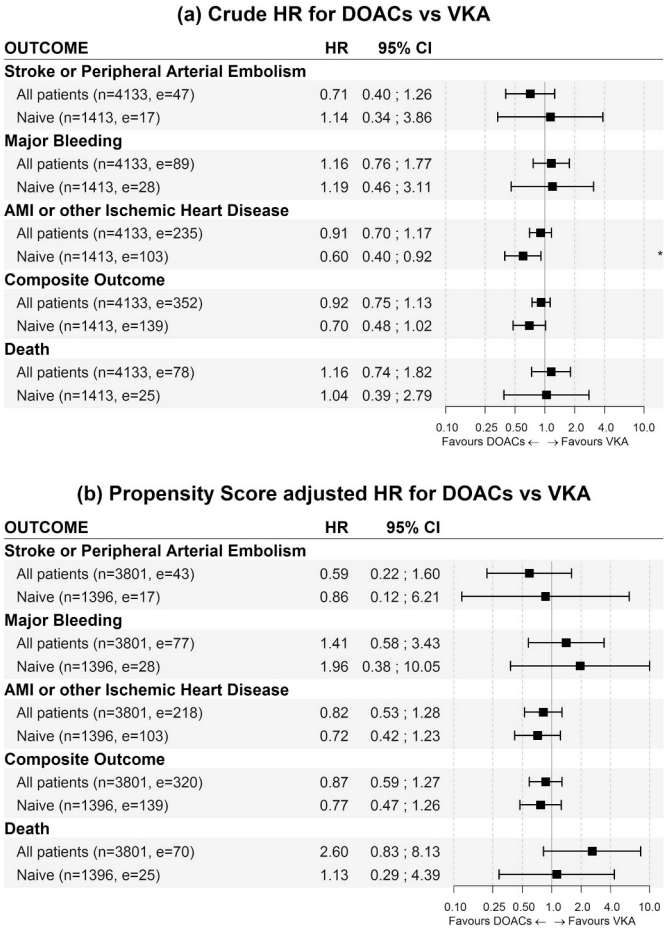

Fig. 1. Effectiveness and safety of DOACs vs. VKAs: unadjusted and PS-adjusted analysis.

2.8.5. Propensity score

In order to take into account unbalances in baseline characteristics, we also provided estimates based on propensity score methods [26–28]. This "PS-adjusted" analysis was only performed in Scenario 1.

The propensity score was the standardized logit-transformed individual probability of receiving DOACs, calculated on the basis of baseline patient characteristics. A multivariable logistic model was used to estimate these probabilities; the dependent variable was DOACs use (yes vs no), while independent variables were those recorded at enrollment. Pairwise interactions as well as b-spline terms for continuous variables were used to develop the propensity score model.

The PS-adjusted estimates were calculated using the propensity score covariate adjustment method [27,28], which consists in estimating an FG model, by using cohort and propensity score as independent variables. In order to manage non-linear relationships between outcome risk and propensity score, the latter was included in the model via a b-spline quadratic transformation.

After PS estimation, the balance of the recorded characteristics at baseline, between VKAs and DOACs cohorts, was assessed by means of effect size measures. We calculated conditional weighted standardized

Table 3
Sample characteristics at baseline and concomitant drug use during follow-up, by cohort - Scenario 2.

			Apixaban (n = 954)		Dabigatran (n = 434)		Rivaroxaban (n = 790)	
Demographic characteristics								
Age	Years	mean sd	76.60	8.70	74.46	9.01	74.54	8.88
	≥ 80	n %	372	39.0%	128	29.5%	237	30.0%
Gender	M	n %	492	51.6%	182	41.9%	336	42.5%
Previous VKA or DOACs use								
Experienced	VKA	n %	85	8.9%	27	6.2%	55	7.0%
	DOACs	n %	378	39.6%	191	44.0%	369	46.7%
Naive		n %	491	51.5%	216	49.8%	366	46.3%
CHA_2DS_2-VASc (+)								
Overall score	[0–9]	mean sd	3.55	1.33	3.23	1.31	3.26	1.33
Congestive heart failure	Yes	n %	102	10.7%	50	11.5%	78	9.9%
Hypertension	Yes	n %	803	84.3%	345	79.5%	649	82.5%
Stroke/TIA/Thromboembolism	Yes	n %	104	10.9%	45	10.4%	76	9.7%
Vascular disease	Yes	n %	128	13.4%	43	9.9%	65	8.3%
Diabetes	Yes	n %	183	19.2%	73	16.8%	170	21.6%
Modified HAS-BLED (+)								
Overall score	[0–8]	mean sd	1.83	0.80	1.79	0.78	1.70	0.75
Hypertension	Yes	n %	630	66.1%	287	66.1%	513	65.2%
Renal disease	Yes	n %	43	4.5%	7	1.6%	32	4.1%
Liver disease	Yes	n %	2	0.2%	2	0.5%	5	0.6%
Stroke	Yes	n %	98	10.3%	36	8.3%	48	6.1%
Major bleeding	Yes	n %	46	4.8%	16	3.7%	29	3.7%
Medication	Yes	n %	38	4.0%	21	4.8%	21	2.7%
Alcol or drugs	Yes	n %	13	1.4%	28	6.5%	5	0.6%
Previous hospital admissions								
Congestive heart failure	Yes	n %	155	16.2%	55	12.7%	131	16.6%
Peripheral vascular disease	Yes	n %	42	4.4%	18	4.1%	38	4.8%
Hypertension, uncomplicated	Yes	n %	385	40.4%	151	34.8%	307	38.9%
Hypertension, complicated	Yes	n %	136	14.3%	49	11.3%	105	13.3%
Diabetes, uncomplicated	Yes	n %	110	11.5%	40	9.2%	94	11.9%
Diabetes, complicated	Yes	n %	15	1.6%	10	2.3%	17	2.2%
Liver disease	Yes	n %	19	2.0%	8	1.8%	15	1.9%
Alcol abuse	Yes	n %	2	0.2%	2	0.5%	3	0.4%
Drug abuse	Yes	n %	0	0.0%	0	0.0%	0	0.0%
Other neurological disorders	Yes	n %	20	2.1%	13	3.0%	20	2.5%
Myocardial infarction	Yes	n %	56	5.9%	19	4.4%	52	6.6%
Cerebrovascular disease	Yes	n %	186	19.5%	78	18.0%	118	14.9%
Renal disease	Yes	n %	34	3.6%	8	1.8%	25	3.2%
Concomitant drugs								
Aspirin	Yes	n %	61	6.4%	26	6.0%	47	5.9%
Clopidogrel	Yes	n %	6	0.6%	0	0.0%	8	1.0%
ACE-inhibitors	Yes	n %	280	29.4%	126	29.0%	227	28.7%
Amiodarone	Yes	n %	110	11.5%	44	10.1%	103	13.0%
Statins	Yes	n %	386	40.5%	179	41.2%	317	40.1%
Proton pump inhibitors	Yes	n %	441	46.2%	195	44.9%	337	42.7%
H_2-receptor antagonists	Yes	n %	28	2.9%	8	1.8%	15	1.9%
Beta-blockers	Yes	n %	673	70.5%	311	71.7%	551	69.7%
Heparin	Yes	n %	1	0.1%	0	0.0%	1	0.1%

DOACs = Direct Oral Anticoagulants; VKA = Vitamin K Antagonists; sd = standard deviation; (+) = data was gathered for 953, 434 and 787 patients, respectively.

differences by an already described method [29], which considers the balancing effect of PS. As reference value before PS adjustment, we also reported baseline standardized differences. Reference values for effect sizes were those previously reported [30], being 0.2 equal to a small effect size, 0.5 to a medium effect size and 0.8 to a large effect size. A value < 0.1 suggested a good balance after propensity score estimation [28].

2.8.6. Sub-group analysis

The above mentioned statistical analyses were repeated, only considering the sub-group of naïve patients. Regarding PS estimation, the multivariable logistic model was the same as the principal analysis.

Statistical analyses were performed with SAS/STAT 9.3 software (SAS Institute), considering a 95% confidence level ($p < .05$).

3. Results

3.1. Enrollment

4191 patients gave their written consent to participate in the study. Of them, 4133 (98.6%) were linked to ER Region administrative data sets, 2178 (52.7%) in the DOACs cohort and 1955 (47.3%) in the VKAs cohort. Clinical data at baseline (i.e. CHADS-VASC and HAS-BLED scores) was available for 3801 (92.0%) of them, 2174 (57.2%) in the DOACs and 1627 (42.8%) in the VKAs cohorts. With respect to Scenario 2, 954 (43.9% of all DOACs) patients were in the Apixaban, 434 (20.0%) in the Dabigatran, 790 (36.3%) in the Rivaroxaban cohort. Respectively, 953, 434 and 787 of them had complete clinical information at baseline.

Unadjusted analyses were performed on the whole sample of 4133 patients, while PS-adjusted analysis considered the subsample of 3801 patients with complete baseline data.

Table 4
Incidence outcome rates, by cohort - Scenario 2.

Outcome		Apixaban		Dabigatran		Rivaroxaban	
All patients (n = 4133)							
Effectiveness - primary	e e%p-y	12	1.03	5	0.97	5	0.51
Stroke	e e%p-y	12	1.03	5	0.97	4	0.41
Peripheral arterial embolism	e e%p-y	0	–	0	–	1	0.10
Safety - primary	e e%p-y	29	2.38	10	1.95	12	1.22
Intracranial hemorrhage	e e%p-y	11	0.94	2	0.39	4	0.41
Spinal hemorrhage	e e%p-y	0	–	0	–	1	0.10
Other sites major bleeding	e e%p-y	1	0.09	0	–	1	0.10
Gastrointestinal hemorrhage	e e%p-y	17	1.45	8	1.56	7	0.71
Intraocular hemorrhage	e e%p-y	2	0.09	0	–	0	–
Safety - secondary	e e%p-y	52	4.45	17	3.31	53	5.38
Acute myocardial infarction	e e%p-y	8	0.68	2	0.39	6	0.61
Other ischemic heart disease	e e%p-y	47	4.02	15	2.92	49	4.97
Composite outcome	e e%p-y	87	7.44	30	5.84	67	6.80
Death	e e%p-y	22	1.88	5	0.97	18	1.83
Only naive patients (n = 1413)							
Effectiveness - primary	e e%p-y	8	1.32	2	0.82	4	0.97
Stroke	e e%p-y	8	1.32	2	0.82	3	0.73
Peripheral arterial embolism	e e%p-y	0	–	0	–	1	0.24
Safety - primary	e e%p-y	15	2.48	5	2.06	3	0.73
Intracranial hemorrhage	e e%p-y	7	1.16	1	0.41	2	0.49
Spinal hemorrhage	e e%p-y	0	–	0	–	0	–
Other sites major bleeding	e e%p-y	1	0.17	0	–	1	0.24
Gastrointestinal hemorrhage	e e%p-y	7	1.16	4	1.65	1	0.24
Intraocular hemorrhage	e e%p-y	0	–	0	–	0	–
Safety - secondary	e e%p-y	33	5.45	8	3.30	30	7.28
Acute myocardial infarction	e e%p-y	5	0.83	0	–	3	0.73
Other ischemic heart disease	e e%p-y	29	4.79	8	3.30	28	6.79
Composite outcome	e e%p-y	52	8.59	14	5.77	35	8.49
Death	e e%p-y	9	1.49	5	2.06	5	1.21

e = number of events; e%p-y = number of events per 100 person-years.

3.2. Scenario 1 – all DOACs vs VKAs

Descriptive statistics of VKAs and DOACs cohorts are reported in Table 1.

Study population had a mean age of 76.4 (SD 8.6) years and 39.2% of patients were older than 80 years. The mean CHA_2DS_2-VASc and HASBLED scores were, 3.5 (SD 1.3) and 1.8 (SD 0.8), respectively.

The VKAs cohort statistically differed from the DOACs one, in terms of proportion of male subjects (57.4% vs 53.6%), mean age (77.4 vs 75.4 years), CHA_2DS_2-VASc (3.7 vs 3.4) and HAS-BLED mean scores (1.9 vs 1.8). Moreover, the two cohorts differed in terms of patients naïve to any anticoagulant: 17.5% in VKAs cohort vs 49.3% in DOACs cohort.

In terms of concomitant use of antiplatelet agents, we found no statistical difference between the two cohorts (aspirin, 7.6% vs 6.2% and clopidogrel, 1.2% vs 0.6%). These percentages are lower than those that have been reported in other studies [31,32].

The mean follow-up time was 409 days in VKAs cohort and 457 in DOACs cohort.

During this follow-up period, 430 (10.4%) patients experienced an outcome event, 198 (10.1%) in VKAs and 232 (10.7%) in DOACs cohort. Overall, 3031 (73.3%) patients were alive and event-free at 31-st January 2017, while 189 (4.6%) left the study due to drug switch and 483 (11.7%) for therapy interruption.

Table 2 reports number of events and crude incidence rates stratified by cohort as well as for naïve patients.

The crude incidence rates of stroke or peripheral arterial embolism were 1.14 and 0.81, whereas for bleeding they were 1.69 and 1.91 per 100 person-years in the VKAs and DOACs cohorts, respectively. Regarding safety, the incidence rates of intracranial and gastrointestinal hemorrhages were, respectively, 0.46 and 0.82 per 100 person-years in the VKA and 0.66 and 1.18 per 100 person-years in the DOACs cohorts. Mortality rates were 1.46 and 1.69 per 100 person-years for the VKAs and DOACs patients.

Unadjusted analysis and PS-adjusted analysis results are reported in Fig. 1.

The results from unadjusted analysis showed that the two anticoagulant treatments did not differ in terms of risk of stroke or peripheral arterial embolism (HR = 0.71, 95%CI = 0.40–1.26), bleeding (HR = 1.16, 95%CI = 0.76–1.77), AMI or other ischemic diseases (HR = 0.91, 95%CI = 0.70–1.17), composite outcome (HR = 0.92, 95%CI = 0.75–1.14) and death (HR = 1.16, 95%CI = 0.39–2.79).

Similar results were obtained when the analysis was restricted to naïve patients, except for AMI or other ischemic diseases. Indeed, we observed a lower incidence of AMI in DOACs users (HR = 0.60, 95%CI = 0.40–0.92), when compared to VKAs ones.

The balancing in baseline characteristics after PS adjustment is shown in Appendix II. All baseline characteristics were balanced between VKAs and DOACs cohorts, except for the variables previous use of anticoagulants and HAS-BLED scores, for which imbalance was observed in all-patients and naïve-patients analyses, respectively. However, the extent of the residual imbalances was small and considered tolerable for the purposes of PS analysis.

The results after PS adjustment also showed that the two anticoagulant treatments did not differ in terms of risk of stroke or peripheral arterial embolism (HR = 0.59, 95%CI = 0.22–1.60), bleeding (HR = 1.41, 95%CI = 0.58–3.43) AMI or other ischemic disease (HR = 0.82, 95%CI = 0.53–1.28), composite outcome (HR = 0.87, 95%CI = 0.59–1.27) and death (HR = 2.60, 95%CI = 0.83–8.13).

The same results were observed when the analysis was restricted only to naïve patients.

3.3. Scenario 2 - individual DOACs vs VKAs

Descriptive characteristics of Apixaban, Dabigatran and Rivaroxaban cohorts are reported in Table 3.

Average follow-up time was 409 days in VKAs cohort and 448, 433 and 456 in Apixaban, Dabigatran and Rivaroxaban cohorts,

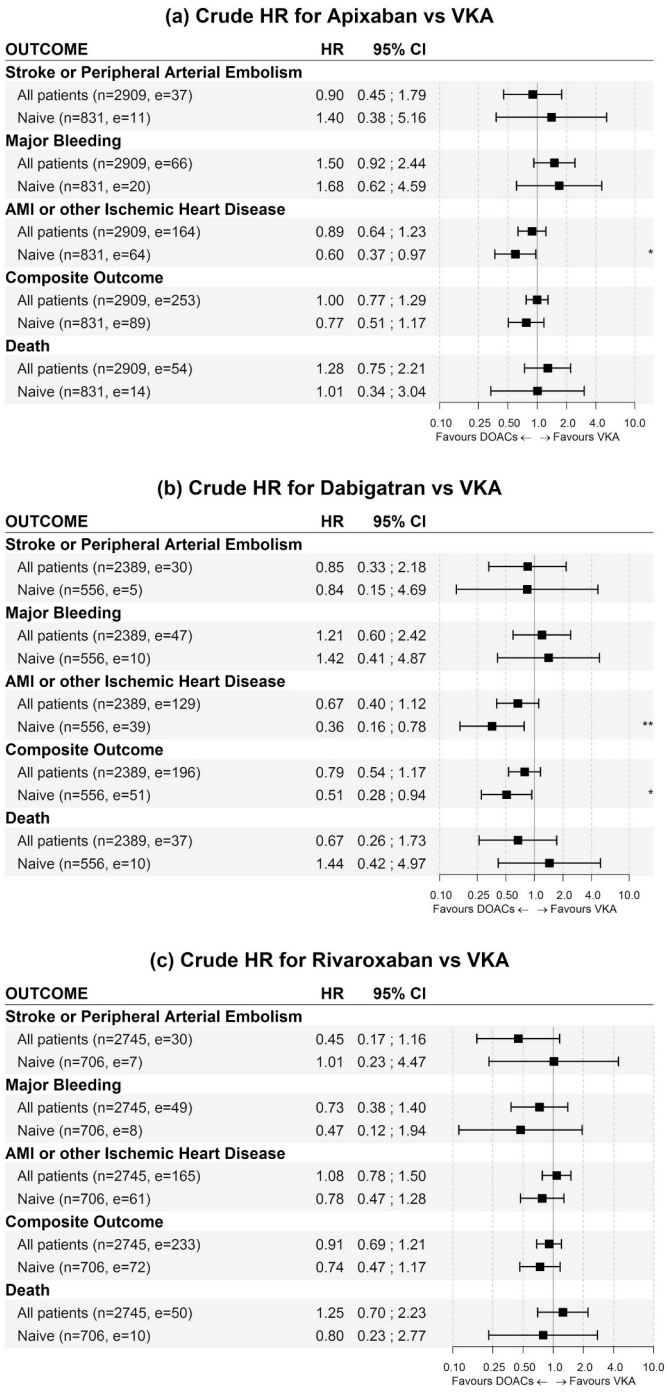

Fig. 2. Effectiveness and safety of single DOACs vs. VKAs: unadjusted analysis.

respectively.

During follow-up, 427 (10.3%) patients experienced an outcome event, 109 (11.4%) in Apixaban, 35 (8.1%) in Dabigatran and 85 (10.8%) in Rivaroxaban cohorts. Overall, 2975 (72.0%) patients were alive and event-free at 31-st January 2017, while 249 (6.0%) left the study due to drug switch and 480 (11.6%) for therapy interruption.

Crude incidence rates of events for the three cohorts are reported in Table 4.

Crude incidence rates for stroke or peripheral arterial embolisms were 1.03, 0.97 and 0.51 per 100 person-years for Apixaban, Dabigatran and Rivaroxaban cohorts, respectively, whereas for bleeding they were 2.38, 1.95 and 1.22 per 100 person-years.

Moreover, incidence rates of intracranial and gastrointestinal hemorrhages were 0.94 and 1.45 per 100 person-years in the Apixaban, 0.39 and 1.56 per 100 person-years in the Dabigatran and 0.41 and 0.71 per 100 person-years in the Rivaroxaban cohorts, respectively.

Mortality rates were 1.88, 0.97 and 1.83 per 100 person-years for the Apixaban, Dabigatran and Rivaroxaban patients, respectively.

The results of the unadjusted analysis comparing effectiveness and safety of single DOACs vs. VKAs are reported in Fig. 2.

Briefly, no differences were found in the unadjusted analysis between Apixaban, Dabigatran and Rivaroxaban as individually compared to VKA in terms of outcomes. Similar results were observed if the analysis was restricted only to naïve patients, except for the secondary end-point of AMI or other ischemic disease. Indeed, we observed a lower incidence of AMI in DOACs respect to VKA users in the Apixaban and Dabigatran cohorts (HR = 0.60, 95%CI = 0.37–0.97 and HR = 0.36, 95%CI = 0.16–0.78, respectively). Moreover, the risk of the composite outcome was lower in Dabigatran cohort, as compared to VKAs cohort, only in naïve patients (HR = 0.51, 95%CI = 0.28–0.94).

3.4. Time in therapeutic range

We measured Time in Therapeutic Range (TTR) in the 6 months before the end of the follow-up periods. Mean TTR was 74.0, while 77.8% patients had TTR > 60%, denoting a good level of VKA therapy control.

3.5. DOACs estimated adherence

For each DOACs patient, we estimated adherence to the prescribed therapy as the ratio between prescribed pills and those expected to be taken on the basis of follow-up duration. Mean estimated adherence was 94.0%, while 20.2% patients had adherence lower than 90%, denoting a high level of patient's adherence.

4. Discussion

The results of this prospective study showed that in a context of a well-managed VKA anticoagulant treatment, with a mean TTR > 70%, VKAs and DOACs didn't differ with respect to effectiveness and safety.

We observed a low incidence of either thrombotic and hemorrhagic events in both cohorts.

Several observational studies [31] have shown that patients treated with DOACs have less major bleeding events, compared to those treated with VKA. However, our study did not find such a difference, either in the whole cohort or if only naïve patients were considered, according to other ones mainly focused on patients switching to DOAC from warfarin [32–34].

Regarding intracranial hemorrhages (ICH), most of previous studies showed a greater safety of DOACs respect to VKAs, however in our study we didn't observe such a difference. This result may be explained by the high rate of ICH observed in the Apixaban-treated group and/or by the small absolute number of outcome events, which cannot rule out a casual effect.

However, in evaluating such findings, it is important to underline that we included both naïve and experienced patients, while most of previous studies considered only naive patients. Therefore, our study population can be considered more representative of every day clinical practice, with a potential “depletion of susceptible” patients to serious adverse events among VKA users.

Nevertheless, analyses carried out on the whole population and on naive patients showed similar results regarding effectiveness and safety.

The main strengths of our study are: its prospective cohort design and the involvement of a regional network of centers highly homogeneous regarding to their expertise in the use of DOACs and VKAs, as they shared a protocol for the management of anticoagulant therapies in NVAF patients. Indeed, when DOACs became available in Italy in 2013, the ER Health Authority settled up a clinical governance program

aimed at improving anticoagulant treatment with DOACs. This goal was pursued by releasing a steering document about the use of DOACs in the clinical practice, regularly updated [35] and by setting up a regional registry of DOACs treatment.

Also, the use of several data sources and of record-linkage techniques allowed us to collect a wide range of demographic and clinical data, including those on quality of VKA treatment, such as TTR. Furthermore, the information on outcomes was gathered from administrative healthcare databases, allowing a standardized and reliable data collection.

Finally, the use of PS methods combined with competing risks time-to-event regression, allowed us to provide estimates of treatment effects, which are less prone to biases.

Some limitations of our work should also be discussed.

First, we are aware that our study's sample size is not large enough if compared to other prospective ones published in the literature. Consequently, we decided against performing PS in Scenario 2. However, this figure represents the number of patients that we could include over the time frame of two years in which enrollment was carried out.

Moreover, we did not record informations about DOACs dosage.

Furthermore, our study was limited to the three DOACs that were in use in Italy at the time of study approval, leaving unanswered questions regarding Edoxaban effectiveness and safety.

5. Conclusions

Our study suggests that, in a healthcare context ensuring optimal management of VKA treatment, DOACs and VKAs do not differ in terms of effectiveness and safety in NVAF patients. Further prospective studies with larger sample sizes are needed to confirm such findings.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejim.2018.12.010.

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