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Real-world 2-year outcome of atrial fibrillation treatment with dabigatran, apixaban, and rivaroxaban in patients with and without chronic kidney disease

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Abstract

Patients with non-valvular atrial fibrillation (NVAF) and chronic kidney disease (CKD) are at increased risk of stroke and bleeding. Although direct oral anticoagulant (DOAC) trials excluded patients with severe CKD, a growing portion of CKD patients have been starting DOACs and limited data from real-world outcome in this high-risk setting are available. The INSigHT registry included 632 consecutive NVAF patients that started apixaban (256 patients, 41%), dabigatran (245, 39%) and rivaroxaban (131, 20%) between 2012 and 2015. Based on creatinine clearance, two sub-cohorts were defined: (1) non-CKD group (CrCl 60–89 mL/min, 413 patients) and (2) CKD group (15–59 ml/min, 219). Compared to non-CKD patients, those with CKD, were at higher ischemic (CHA_2DS_2-VASc 4.5 vs 2.9, $p<0.001$) and hemorrhagic risk (HAS-BLED 2.4 vs 1.8, $p<0.001$). At 2-year follow-up, the overall ISTH-major bleeding and thromboembolic event rates were 5.2% and 2.3% and no significant difference between non-CKD and CKD patients for both efficacy and safety endpoints were observed. In non-CKD patients, the 2-year ISTH-major bleeding rates were higher in rivaroxaban group (HR 2.9, 95% CI 1.1–7.3; $p=0.047$) while dabigatran showed non-significant excess in thromboembolic events (HR 4.3, 95% CI 0.9–20.8; $p=0.068$). In CKD patients, a significantly higher rate of thromboembolic events was observed in rivaroxaban (HR 6.3, 95% CI 1.1–38.1; $p=0.044$). This real-world, non-insurance database registry shows remarkable 2-year safety and efficacy profile of DOACs even in patients with moderate to severe CKD. Head to head differences between DOACs are exploratory, hypothesis generating and warrant further investigation in larger studies.

Keywords Non-valvular atrial fibrillation · Direct oral anticoagulant · Chronic kidney disease

Introduction

Prevalence of atrial fibrillation is higher in patients with chronic kidney disease (CKD) [1, 2] which are at increased risk of stroke and bleeding compared to those with normal renal function [3, 4]. Despite initial doubts, warfarin has showed a positive net clinical impact, reducing mortality and is warranted in this setting [5, 6]. However, warfarin is associated with poor time in therapeutic in range (TTR) and high bleeding risk in CKD [4, 7]. Direct oral anticoagulants (DOACs), which are increasingly prescribed [8], have good safety and efficacy profiles compared to warfarin in moderate to severe renal impairment not requiring hemodialysis [9]. However, each DOAC is eliminated via the kidneys to some degree: approximately 80% for dabigatran, 26% for apixaban, 33% for rivaroxaban and 50% for edoxaban.

Cosmo Godino and Francesco Melillo contributed equally to this work and can be considered as co-first author.

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Appropriate dosing reduction indication are available for each drug with different cutoff values based on renal function, age and body weight [10]. The European Society of Cardiology guidelines should be strictly followed because a mortality increase with low-dosing regimens of apixaban and rivaroxaban compared to warfarin has recently been described in some real-word clinical reports, where inappropriate dosing may be used [11]. Phase III randomized trials excluded patients with creatinine clearance less than 30 ml/min (ROCKET [12], RE-LY [13] and ENGAGE [14]) or less than 25 ml/min (ARISTOTLE [15]); therefore, patients with impaired renal function represent only a small part of the studied populations. Nowadays, a growing portion of CKD patients have been starting on DOAC but, to the best of our knowledge, there are limited "real world" data regarding their use in this high-risk setting of patients. Therefore, the aim of the INSigHT registry is to report 2-year third level care center experience using dabigatran, apixaban and rivaroxaban in stage III-IV CKD patients with non-valvular atrial fibrillation for thromboembolic event prevention.

Methods

Population

The Italian NOACs San Raffaele HospiTal (INSigHT) registry is an observational, multidisciplinary, non-insurance database study that included all consecutive patients with non-valvular atrial fibrillation that started, either anticoagulation-naïve or switched from vitamin K antagonist, dabigatran (introduced in 2010), rivaroxaban (introduced in 2011) or apixaban (introduced in 2012), at San Raffaele hospital between January 2012 and December 2015. Patients recently treated with edoxaban (introduced in August 2016) were not included in the present analysis. All DOACs were restricted to reduced doses approved for stroke prevention in atrial fibrillation (in Europe) in elderly people and those with CKD according to differences in guidelines criteria for recommendation: apixaban 2.5 mg, dabigatran 110 mg, and rivaroxaban 15 mg. To ensure the correct use of DOACs, the clinical management was based on the most updated recommendations [16]. To ensure the correct use of DOACs, the clinical management was based on the most updated recommendations [17]. To focus on non-valvular atrial fibrillation, we excluded patients with previous hospital diagnoses indicating valvular atrial fibrillation (moderate to severe mitral stenosis or mechanical heart valves). We further excluded patients aged < 18 years, with previous cancer diagnosis and all those with an indication for oral anticoagulant treatment other than atrial fibrillation (pulmonary embolism, deep venous thrombosis, or recent hip/knee surgery) and those with incomplete data collection or with end-stage renal disease requiring hemodialysis. *CKD* was defined as kidney damage or decreased kidney function for three or more months and classified according to creatinine clearance (CrCl) levels (calculated using the Cockcroft–Gault formula, which has been used in all phase III NOAC trials): CrCl between 59 and 30 ml/min and between 29 and 15 ml/min identified patients with *moderate and severe CKD*, respectively. Two sub-cohorts were defined based on renal function: (1) patients with normal renal function or mild decreased CrCl (60–89 mL/min) were included in the non-CKD group; (2) patients with moderately or severely impaired renal function (CrCl 15–59 ml/min), were included in the CKD group. Patients were required to have at least 3 months of continuous treatment to be included in the study. All patients signed informed consent and the study was approved by the Institutional Committee of Human Research at our Hospital.

Endpoint definition

The *primary efficacy endpoint* was the 2-year rate of systemic thromboembolism (including ischaemic stroke, transient ischemic attack, systemic embolism and myocardial infarction). The *primary safety endpoint* was the 2-year rate of major bleeding, defined according to the International Society of Thrombosis and Hemostasis criteria (ISTH) [18]. Overall bleedings were recorded, including minor bleeding, gastrointestinal, intracranial, symptomatic and fatal bleeding. Overall death, cardiovascular death and treatment discontinuation (either shift to other anticoagulant treatment or permanent drug withdrawal) were considered as *secondary endpoints*. For quantifying thromboembolic risk, we combined comorbidity information into the CHA_2DS_2-VASc; similarly, to assess the risk of bleeding we calculated the HAS-BLED score. Baseline clinical characteristics including age, gender, body mass index, date of treatment start, dosing regimen, prior bleeding or ischaemic events, comorbidities (hypertension, diabetes, congestive heart failure, vascular disease, liver disease, chronic obstructive lung disease), laboratory findings (creatinine and hemoglobin levels, platelet number) and concurrent medication (antithrombotic, antiarrhythmic) or any prior antithrombotic treatment were collected.

Data collection

Information retrieval techniques were utilized by a database specialist (DBA) for match search data into the overall hospital database, considering all patients on DOACs discharged from different units and departments (cardiology, interventional cardiovascular and arrhythmia units, internal medicine and neurology department, Fig. 1) in the index period between January 2012 and December 2015.

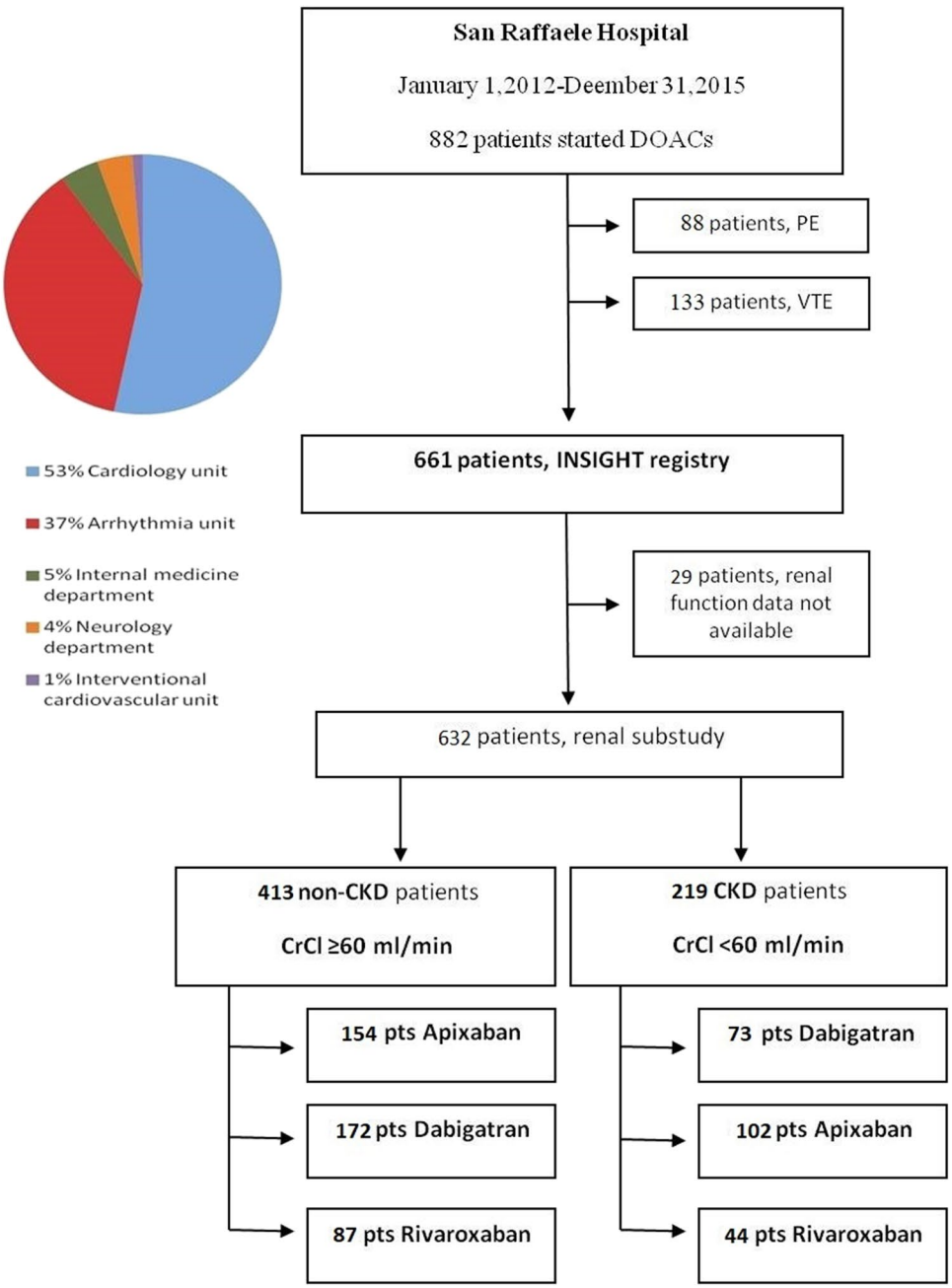

Fig. 1 Distribution of patients on DOACs discharged from different units and departments and study flow chart. PE = pulmonary embolism; VTE = venous thromboembolism

Two data operators, Fuzzy Lookup and Fuzzy Grouping, [19] were applied to resulting datasets for data cleaning. The clinical observation started at the time when patients initiated DOACs. A dedicated non-insurance database for pre-specified data entry and clinical-event endpoint adjudication has been used to avoid selection bias or incomplete data reports. For data entry control, completion of at least 95% of clinical forms per each patient to be included in the final analysis was required. Events occurring after a treatment variation (shift to other DOAC, shift to other anticoagulant regimen, interruption) were critically analyzed and adjudicated according to the treatment on going at the time the event happened. All events were reviewed and confirmed by two independent cardiologists (C.G., M.C. and F.M.); in the controversial cases the opinion of a third senior doctor (A.C., A.S, and A.M.) was required.

Statistical analysis

Continuous variables were reported as mean ± standard deviation (SD) or median and compared with Student's *t* test or Mann–Whitney or Wilcoxon tests, on the basis of the normality of the data (which was verified by Kolmogorov–Smirnov goodness-of-fit test). Categorical variables

(such as frequencies or percentages) were compared with $\chi 2$ test without Yates correction for continuity [20] or the Fisher exact test as appropriate [21]. Clinical outcomes and adverse events of the INSigHT registry were prospectively monitored at 6 months, 1 year and at 2 years by ambulatory direct visit, phone interview or contact with the referring physician of each department, and specific hospital files were requested when needed. Event-free survival assessed at 2 years was evaluated according to the unadjusted Kaplan–Meier method and survival among groups were compared using log-rank test (Cox–Mantel test). Clinical follow-up was censored at the date of the last follow-up or at 730 days (2 years), whichever came first, to balance the follow-up time between treatment groups having DOACs been approved in a different time period. Data for patients lost at follow-up were censored at the time of the last contact. Univariate Cox proportional hazards model was utilized to evaluate the association between the adverse events time of patients and the three DOACs covariates. Three different models were used to estimate the hazard ratios (HR) and 95% confidence intervals (CI) of adverse events related to a single DOAC (reference) versus the other two. HR > 1 indicates a covariate positively associated with the adverse event probability, and thus negatively associated with the length of event-free survival. Two-side p values < 0.05 were considered statistically significant. Statistical analysis was performed using SPSS 23 (SPSS Inc., Chicago, IL, USA). Kaplan–Meier survival curves were generated with GraphPad Prism software (version 7.03; GraphPad, Inc, San Diego, CA).

Results

Clinical and medical treatment data

During the index period, a total of 882 patients received indication for a DOACs from the overall San Raffaele database. Of these, 661 patients (75%) were enrolled in the INSigHT registry according to the inclusion/exclusion criteria; for the present analysis, we further excluded 29 patients for whom creatinine clearance was not calculable due to missing data (Fig. 1, study flowchart). A total of 632 patients were finally analyzed: 245 patients were treated with dabigatran (39%), 256 with apixaban (41%) and 131 with rivaroxaban (20%). Patients were stratified in two main sub-cohorts of non-CKD and CKD patients. Baseline clinical and medical treatment characteristics of sub-cohorts are reported in Table 1. Most of baseline clinical characteristics varied markedly between non-CKD and CKD patients. In general, patients with CKD were significantly older ($p < 0.001$), more often women ($p < 0.001$) and with lower BMI ($p < 0.001$). They had more comorbidities such as hypertension ($p = 0.005$), diabetes ($p = 0.005$), peripheral vascular disease ($p < 0.001$), heart failure ($p < 0.001$) and previous bleeding events ($p = 0.012$), reflected in both higher ischemic and hemorrhagic risk as estimated by CHA_2DS_2-VASc score (4.5 ± 1.5 vs 2.9 ± 1.7, $p < 0.001$) and HAS-BLED score (2.4 ± 0.9 vs 1.8 ± 1.1, $p < 0.001$).

In both subgroups of non-CKD and CKD patients, most of baseline clinical characteristics were comparable across exposure to each DOAC (Table 1). Apixaban was the most frequently prescribed DOAC in patients with CKD ($p = 0.054$). Among CKD patients, the average age for apixaban users was significantly higher compared to those on rivaroxaban (80.0 ± 6.5 vs 77.5 ± 7.8 years, $p = 0.05$). In both non-CKD and CKD patients, patients on dabigatran were more frequently on low-dose regimen (110 mg/bid) compared to those on apixaban (2.5 mg/bid) and rivaroxaban (15 mg/od) ($p < 0.001$ and $p = 0.003$, for non-CKD and CKD, respectively). In the overall population, concomitant single oral antiplatelet therapy was present in 112 patients (17.3%), and 21 patients (3.3%) were on triple antithrombotic therapy, with no differences between non-CKD and CKD subgroups.

Among CKD patients, 25 (11%) had a severely reduced renal function (CrCl < 30 ml/min, severe CKD). As compared to those with moderate CKD (CrCl between 59 and 30 ml/1 min), patients with severe CKD were older (84.0 ± 6.6 vs 78.2 ± 8.2 years; $p < 0.001$) and with extremely high ischemic (CHA_2DS_2-VASc score, 5.9 ± 1.6 vs 4.3 ± 1.4, $p = 0.001$) and hemorrhagic risk (2.7 ± 0.8 vs 2.3 ± 0.8, $p = 0.025$).

Complete matched data on renal function at follow-up were available for a subset of patients ($n = 102$, 16.1%). We observed a non-significant decline of overall mean creatinine clearance values up to 2 years (from 70.9 ± 28.1 to 67.5 ± 30.3 ml/min, $p = 0.06$), with a mean decline of 1.67 ml/min per year. In the specific, four patients improved the CKD class from moderate to normal and two patients from severe to moderate. Four patients developed moderate CKD and seven patients developed severe CKD (see supplementary appendix Figure).

Two-year clinical outcome

At 2-year follow-up, available in 90% of overall patients, 13 patients (2.3%) experienced a systemic thromboembolic event (*primary efficacy endpoint),* 2.5% in CKD patients and 2.2% in non-CKD patients. Of these, seven patients (1.2%) suffered from an ischemic stroke (Table 2). In terms of safety endpoints, the overall ISTH-major bleeding rate occurred in 29 patients (5.1%), 5.0% in CKD patients and 5.2% in non-CKD patients. Two intracranial bleeding were reported in CKD patients (1%) and two in non-CKD patients (0.5%). Notably, only one fatal bleeding occurred in a CKD patient

Table 1 Baseline clinical characteristics of non-CKD and CKD patients and subgroups stratified by DOAC treatment

	Non-CKD patients					CKD patients					
	Overall $N=413$	Dabigatran $N=172$	Apixaban $N=154$	Rivaroxaban $N=87$	p value (subgroups)	Overall $N=219$	Dabigatran $N=73$	Apixaban $N=102$	Rivaroxaban $N=44$	p value (subgroups)	p value (non-CKD vs CKD)
Age (years), mean ± SD	68.0 ± 11.3	67.8 ± 10.9	69.2 ± 12.0	66.2 ± 10.7	0.155	78.8 ± 8.3	78.0 ± 10.2	80.0 ± 6.5	77.5 ± 7.8	0.135	**< 0.001**
BMI, mean ± SD	27.2 ± 4.3	27.3 ± 4.6	27.4 ± 4.4	26.9 ± 3.5	0.812	24.9 ± 3.8	24.2 ± 3.9	25.4 ± 3.8	24.6 ± 3.5	0.170	**< 0.001**
Female gender, *n* (%)	123 (29.1)	53 (30.1)	48 (30.4)	22 (25.0)	0.629	108 (48.1)	36 (48.0)	51 (48.6)	21 (47.7)	0.995	**< 0.001**
CrCl (mL/min), mean ± SD	95.1 ± 29.9	93.3 ± 25.5	95.0 ± 31.8	98.8 ± 34.4	0.380	44.1 ± 10.6	45.7 ± 10.1	43.4 ± 11.0	42.7 ± 10.7	0.227	**< 0.001**
Low dose, *n* (%)	128 (30.3)	85 (48.3)	39 (24.7)	4 (4.5)	**< 0.001**	138 (61.6)	58 (77.3)	56 (53.3)	24 (54.4)	**0.003**	**< 0.001**
Existing comorbidities, *n* (%)											
Hypertension	309 (73.1)	124 (70.5)	121 (76.6)	64 (72.7)	0.447	186 (83.0)	59 (78.7)	88 (83.8)	39 (88.6)	0.360	**0.005**
Diabetes mellitus	64 (15.2)	25 (14.2)	23 (14.6)	16 (18.2)	0.672	54 (24.1)	17 (22.7)	26 (24.8)	11 (25.0)	0.938	**0.005**
COPD	41 (9.7)	15 (8.5)	16 (10.1)	10 (11.4)	0.745	27 (12.1)	10 (13.3)	10 (9.5)	7 (15.9)	0.753	0.095
Peripheral vascular disease	157 (37.2)	65 (36.9)	62 (39.2)	30 (34.1)	0.772	123 (54.9)	33 (44.0)	61 (58.1)	29 (65.9)	**0.045**	**< 0.001**
Previous stroke/TIA/SE	67 (15.9)	32 (18.2)	24 (15.2)	11 (12.5)	0.471	40 (17.9)	10 (13.3)	21 (20.0)	9 (20.5)	0.454	0.519
Heart failure	43(10.2)	18 (10.2)	15 (9.5)	10 (11.4)	0.897	73 (32.7)	24 (32.2)	36 (34.0)	13 (29.5)	0.823	**< 0.001**
Previous bleeding	44 (10.5)	18 (10.3)	14 (8.9)	12 (13.8)	0.489	39 (17.5)	13 (17.3)	21 (20.2)	5 (11.4)	0.433	**0.012**
Prior AMI	52 (12.4)	19 (10.8)	22 (14.0)	11 (12.5)	0.672	34 (15.3)	11 (14.7)	17 (16.5)	6 (13.6)	0.890	0.294
Bioprosthetic heart valve, *n* (%)	3 (0.7)	1 (0.6)	0 (0)	2 (2.3)	0.122	6 (2.7)	2 (2.7)	3 (2.9)	1 (2.3)	0.980	**0.042**
CHA_2DS_2-VASc score, mean ± SD	2.9 ± 1.7	2.9 ± 1.7	3.1 ± 1.7	2.6 ± 1.6	0.155	4.5 ± 1.5	4.3 ± 1.5	4.7 ± 1.4	4.6 ± 1.6	0.146	**< 0.001**
HAS-BLED score, mean ± SD	1.8 ± 1.1	1.8 ± 1.1	1.9 ± 1.0	1.8 ± 1.0	0.775	2.4 ± 0.9	2.2 ± 0.8	2.5 ± 0.9	2.3 ± 0.8	0.167	**< 0.001**
Prior use of VKA, *n* (%)	189 (45.2)	91 (52.6)	64 (40.8)	34 (38.6)	**0.037**	112 (50.7)	44 (58.7)	48 (47.1)	20 (45.5)	0.203	0.188

Table 1 (continued)

	Non-CKD patients					CKD patients					
	Overall $N=413$	Dabigatran $N=172$	Apixaban $N=154$	Rivaroxaban $N=87$	*p* value (subgroups)	Overall $N=219$	Dabigatran $N=73$	Apixaban $N=102$	Rivaroxaban $N=44$	*p* value (subgroups)	*p* value (non-CKD vs CKD)
Drugs, *n* (%)											
SAPT	66 (15.6)	27 (15.3)	25 (15.8)	14 (15.9)	0.990	46 (20.5)	11 (14.7)	28 (26.7)	7 (15.9)	0.101	0.118
DAPT	14 (3.3)	5 (2.8)	3 (1.9)	6 (6.8)	0.107	7 (3.1)	2 (2.7)	1 (1.0)	4 (9.1)	**0.032**	0.896

Statistically significant p values (< 0.05) are in bold

CKD chronic kidney disease, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *AMI* acute myocardial infarct, *SAPT* single antiplatelet therapy, *DAPT* double antiplatelet therapy

treated with dabigatran. Definitely, there were no significant differences between non-CKD and CKD patients for efficacy endpoints. Similarly, no differences were evident in terms of ISTH-major bleeding, intracranial and gastrointestinal bleeding, but overall bleeding events were significantly higher in CKD patients ($p=0.026$). However, when considering anticoagulation-naïve patients, a higher rate of overall bleeding was detected in CKD versus non-CKD group (22.6 vs 12.8%, $p=0.027$). Two-year all-cause death incidence was significantly higher in CKD versus non-CKD group (9.0 vs 3.8%, $p=0.010$).

A trend towards higher anticoagulation treatment interruption in non-CKD group (23.8 vs 18.6%, $p=0.156$) was evident; conversely, and the proportion of patients who shifted to other anticoagulation regimen was slightly higher in CKD group (7.4% vs 12.1%, $p=0.067$).

In the group of patients with CKD, those with severe CKD (CrCl < 30 ml/min), as compared to patients with moderate CKD (CrCl 31–60 ml/min) experienced higher rates of overall bleeding (32% vs 15.5%, $p=0.046$) without increase in ISTH-major bleeding or intracranial bleeding events, despite the high bleeding risk. A trend towards higher thromboembolic event rate (8.0% vs 1.7%, $p=0.061$) was evident.

Two-year clinical outcome of patients stratified in the three DOAC type groups of treatment

In CKD group, patients on dabigatran did not experience any thromboembolic events. A significantly higher rate of systemic thromboembolic events was witnessed in the rivaroxaban patients compared to those on dabigatran and apixaban (HR 6.3, 95% CI 1.1–38.1; $p=0.044$) (Table 2 and Fig. 2, Panel A). However, when considering ischemic stroke alone, no difference was evident. The 2-year ISTH-major bleeding rate was similar between DOAC subgroups (Fig. 2, Panel C). Although the mean HAS-BLED score was high in all DOAC CKD subgroups, only two intracranial bleeding were reported (one with dabigatran and one in rivaroxaban), one of which resulted in exitus. The discontinuation rates, either due to a shift to other anticoagulant drug or permanent anticoagulant treatment withdrawal, were similar in all three DOAC CKD subgroups.

In non-CKD patients, dabigatran was associated with non-significantly higher thromboembolic event rate (HR 4.3, 95% CI 0.9–20.8; $p=0.068$) (Fig. 2, panel B). All thromboembolic events in dabigatran group occurred in patients on 110 mg × 2 dose regimen. However, no differences were evident in terms of ischemic stroke. Rivaroxaban was associated with significantly higher ISTH-major bleeding risk (4.3% vs 3.1% and 10.8%, dabigatran, apixaban and rivaroxaban, respectively, HR 2.9, 95% CI 1.1–7.3; $p=0.047$) (Table 2 and Fig. 2, Panel D). Notably,

Table 2 Two-year follow-up of non-CKD and CKD patients and subgroups stratified by DOAC treatment

	Non-CKD patients					CKD patients					
	Overall $N=365$	Dabigatran $N=162$	Apixaban $N=129$	Rivaroxaban $N=74$	p value (sub-groups)	Overall $N=199$	Dabigatran $N=70$	Apixaban $N=90$	Rivaroxaban $N=39$	p value (sub-groups)	p value (non-CKD vs CKD)
Thromboembolic events (stroke, TIA, SE and MI), *n* (%)	8 (2.2)	7 (4.3)	0 (0)	2 (2.7)	0.068	5 (2.5)	0 (0)	2 (2.2)	3 (7.7)	**0.044**	0.941
Ischaemic stroke	5 (1.4)	4 (2.5)	0 (0)	1 (1.4)	0.211	2 (1.0)	0 (0)	1 (1.1)	1 (2.6)	0.394	0.526
Ischaemic stroke with hemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	Na	0 (0)	0 (0)	0 (0)	0 (0)	Na	Na
TIA	2 (0.5)	1 (0.6)	0 (0)	1 (1.4)	0.445	2 (1.0)	0 (0)	1 (1.1)	1 (2.6)	0.437	0.442
MI	2 (0.5)	2 (1.2)	0 (0)	0 (0)	0.289	0 (0)	0 (0)	0 (0)	0 (0)	Na	0.418
SE	1 (0.3)	1 (0.6)	0 (0)	0 (0)	0.534	1 (0.5)	0 (0)	0 (0)	1 (2.6)	0.126	0.582
All-cause death, *n* (%)	14 (3.8)	5 (3.1)	8 (6.2)	1 (1.4)	0.173	18 (9.0)	6 (8.6)	10 (11.1)	2 (5.1)	0.572	**0.010**
Cardiac death	5 (1.4)	1 (0.6)	4 (3.1)	0 (0)	Ns	6 (5.5)	3 (7.1)	3 (6.1)	0 (0)	0.522	0.154
Bleeding	0 (0)	0 (0)	0 (0)	0 (0)	Na	1 (0.5)	1 (1.4)	0 (0)	0 (0)	0.398	0.176
Cancer	3 (0.8)	2 (1.2)	1 (0.8)	0 (0)	0.637	3 (1.5)	1 (1.4)	1 (1.1)	1 (2.6)	0.825	0.405
Other	6 (1.6)	2 (1.2)	3 (2.3)	1 (1.4)	0.723	13 (6.5)	3 (4.3)	9 (10.0)	1 (2.6)	0.195	**0.002**
Bleeding, *n* (%)	42 (11.5)	16 (9.9)	14 (10.9)	12 (16.2)	0.325	35 (17.6)	14 (20.0)	14 (15.6)	7 (17.9)	0.848	**0.026**
Major bleeding (ISTH)	19 (5.2)	7 (4.3)	4 (3.1)	8 (10.8)	**0.047**	10 (5.0)	4 (5.7)	2 (2.2)	4 (10.3)	0.157	0.912
Intracranial bleeding	2 (0.5)	0 (0)	1 (0.8)	1 (1.4)	0.385	2 (1.0)	1 (1.4)	1 (1.1)	0 (0)	0.787	0.487
Gastrointestinal bleeding	26 (7.1)	10 (6.2)	7 (5.4)	9 (12.2)	0.159	12 (6.0)	3 (4.3)	5 (5.6)	4 (10.3)	0.397	0.823
Fatal bleeding	0 (0)	0 (0)	0 (0)	0 (0)	Na	1 (0.5)	1 (1.4)	0 (0)	0 (0)	0.396	0.176
Drug discontinuation, *n* (%)											
Shift to other DOACs	27 (7.4)	20 (12.4)	3 (2.3)	4 (5.4)	**0.005**	24 (12.1)	10 (14.3)	10 (11.1)	4 (10.3)	0.818	0.067
Interruption	87 (23.8)	37 (22.8)	27 (20.9)	23 (31.1)	0.290	37 (18.6)	14 (20.0)	15 (16.7)	8 (20.5)	0.877	0.151

Statistically significant p values (< 0.05) are in bold

TIA transient ischaemic attack, *SE* systemic embolism, *MI* myocardial infarct [*p* values generated by log-rank (Mantel Cox) test]

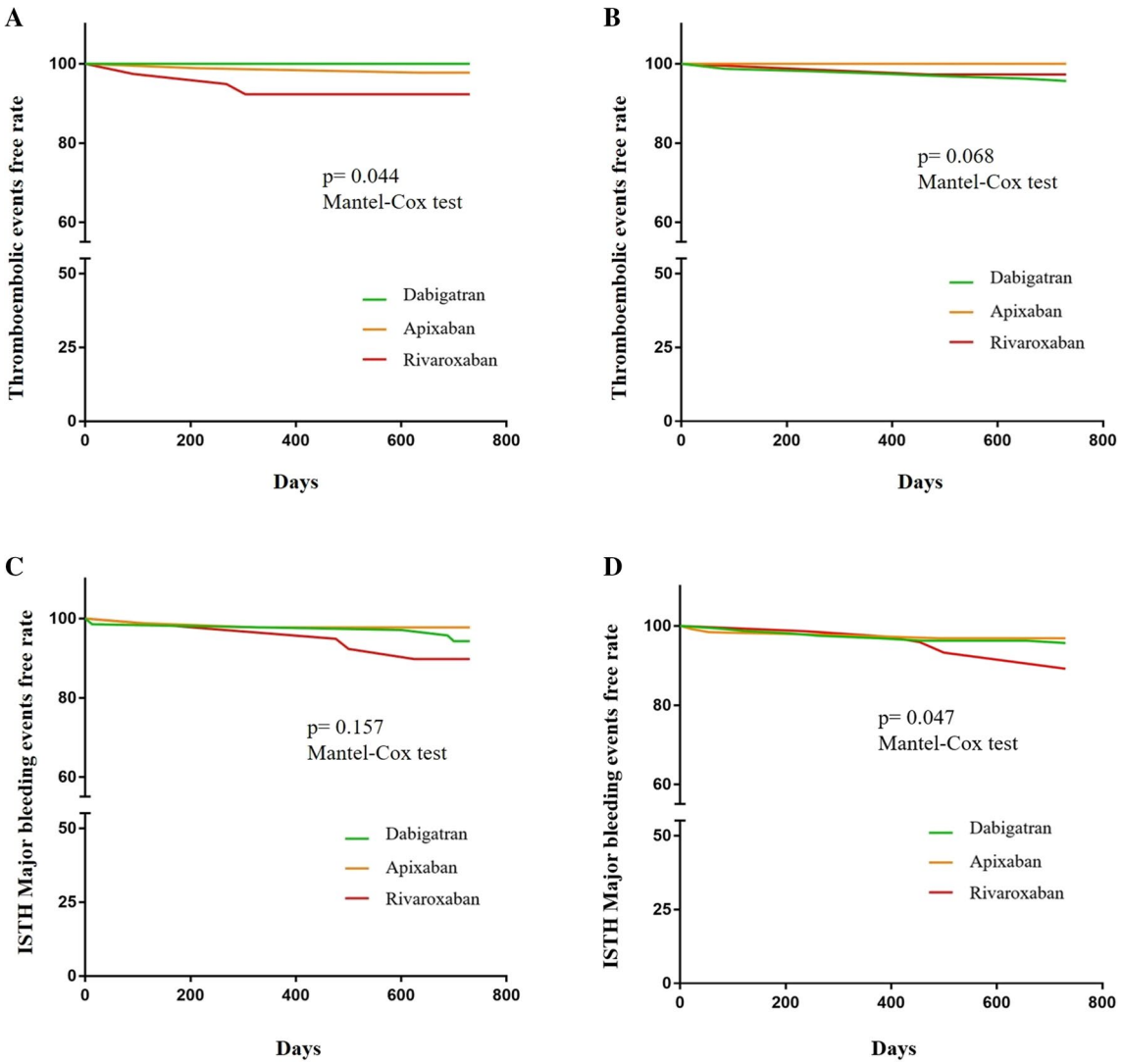

Fig. 2 Kaplan–Mayer analysis of thromboembolic events in CKD (panel A) and non-CKD patients (panel B) and ISTH-major bleeding events in CKD (panel C) and non-CKD patients (panel D) [*p* values generated by log-rank (Mantel Cox) test]

most of rivaroxaban ISTH-major bleeding events were of gastrointestinal origin. However, no fatal bleeding occurred and only two patients were admitted to the emergency department for intracranial hemorrhage (patient on apixaban and rivaroxaban). In terms of treatment persistence, more patients on dabigatran shifted to other DOAC therapy as compared to the other two groups ($p = 0.005$). Conversely, the proportion of patient who permanently discontinued DOAC treatment was quite similar in all subgroups. To the purpose of the safety and efficacy 2-year analysis, no hemorrhagic or thromboembolic events were reported in patients who shifted to other DOAC. Finally, with regard to 2-year cardiac death rates no difference was reported between the three DOAC subgroups in both CKD and non-CKD patients.

Discussion

The present study provides the first-time real-world non-insurance database experience reporting the use of DOACs for thromboembolic events prevention in patients with non-valvular atrial fibrillation stratified for the presence or not of moderate to severe CKD.

The main findings of this single-center, multidisciplinary-independent analysis can be summarized as follows: (1) all direct oral anticoagulants showed remarkable safety and efficacy profile in both CKD and non-CKD patients; (2) in CKD patients, a higher rate of thromboembolic events were observed in the rivaroxaban group, while low dose of dabigatran (110 mg bid) showed slight

excess of thromboembolic events in non-CKD group. (3) In non-CKD patients, ISTH-major bleedings, most of which of gastrointestinal origin, were higher in patients on rivaroxaban.

CKD increases both thromboembolic and bleeding risk in atrial fibrillation and anticoagulation with warfarin is associated with higher 1-year risk of embolic and bleeding events (6.8% and 8.7%, respectively) as previously reported in a Danish nationwide registry [22]. Despite only a small proportion of warfarin is eliminated through glomerular filtration, it would not be an optimal choice for CKD patients as there is evidence of a direct damage on kidney induced this kind of drug [23–25].

Moreover, progression of CKD over time is itself associated to thrombotic and bleeding complications [23]. In this setting, DOACs are associated with lower decline of renal function as compared to warfarin, as shown in sub-analysis of RELY and ROCKET [26–28]. We observed a non-significant decline in creatinine clearance values up to 2 years, with a small proportion of patients developing severe CKD. However, given the relatively small size of the subgroup analyzed, larger studies are needed to properly assess the modification of renal function in real-world patients treated with DOACs.

Although a meta-analysis of DOAC phase III trials in CKD patients showed that both thromboembolic (3.9% vs 5.3%, OR 0.72) and bleeding events (6.8% vs 7.2%, OR 0.82) were significantly lower on DOACs compared to warfarin [29] and a recent population-based cohort study of UK patients with CKD suggested that DOACs are as effective and safe as warfarin [30], the question regarding the choice of the optimal drug among DOACs in this high-risk patients remains still unanswered. In this study, we observed that apixaban was the most frequently used DOACs in the CKD group reflecting clinicians' confidence with the drug in this setting as confirmed by recent ESC recommendations [31]. As evident in the 2-year outcome analysis of patients stratified in the two sub-cohorts, no statistically difference was observed for both ISTH-major bleeding and thromboembolic events between CKD and non-CKD patients, although baseline clinical characteristics and ischemic and hemorrhagic risks markedly varied between the two groups, encouraging the use of DOACs in this high-risk setting of patients.

Interestingly, the rate of overall ISTH-major bleeding with DOACs in CKD patients (2-year rate = 5.0%) was lower compared to the overall bleeding rate of patients with CKD reported in the metanalysis on DOAC phase III trials (1-year rate 4.8%) [9]. We reported only two intracranial bleedings despite the cohort was not at low bleeding risk (mean HAS-BLED score 2.4). Although dabigatran has been associated with increase in major hemorrhage with CrCl levels below 50 ml/min (RE-LY trial sub-analysis) [32], we observed a major bleeding rate similar to apixaban and rivaroxaban, possibly because of the high percentage of patients treated with low-dose regimen. The good safety profile was consistent across different degrees of renal impairment: patients with severe reduction in glomerular filtration rate (estimated GFR < 30 ml/min), did not experience major bleeding events and only 1 fatal intracranial bleeding occurred; as this subgroup was represented by only 25 patients, any analysis was intended to be descriptive, but surely represent a first insight into this poor reported population. It is well known that patients with severe CKD required significantly lower warfarin dosages, spent less time with their international normalized ratio within the target range, were at higher risk for overanticoagulation (INR > 4), and at higher risk for major hemorrhage (more than double) compared with patients with no, mild, or moderate CKD [7].

In this study, CKD patients on rivaroxaban experienced higher rates of thromboembolic events compared to patients on apixaban and dabigatran. This information should be carefully handled, considering possible unmeasured confounders between groups, the low rate of the efficacy endpoint in the CKD group (2.5% at 2 years) and also the play of chance. However, the number of ischaemic stroke events did not differ among groups and the overall rate was low (2-year rate 1%). In CKD patients, the overall thromboembolic events rate was 1% and was lower compared to that reported in the post hoc sub-analysis of patients with CKD of phase III trials, accounting for 2.3% (dabigatran 110 mg) and 1.5% (dabigatran 150 mg) in the RELY study [30], 2.2% in the ARISTOTLE [33] and 2.3% in the ROCKET-AF [34]. A recent network meta-analysis identified apixaban as being the most favorable drug with respect to safety and efficacy in CKD, probably because of its low renal clearance [35].

In non-CKD group, patients on dabigatran showed a trend towards higher rates of thromboembolic events, without excess in ischemic stroke. In addition to the aforementioned considerations, attention should be posed on the large use of the low-dose regimen of dabigatran in this group, possibly leading to excess of thromboembolic events. This contributes to the discussion whether the appropriate use of lower (dabigatran) or reduced (apixaban and rivaroxaban) doses is relevant for outcomes [11].

ISTH-major bleeding rates observed in non-CKD patients on rivaroxaban were higher compared to apixaban and dabigatran: notably, most of events were of gastrointestinal origin and rivaroxaban is known to be associated to increased gastrointestinal bleedings [36]. However, the observed rate (5%/year) was higher when compared to that reported in patients with CKD in ROCKET-AF (3.4%/year) [34]. Conversely, apixaban showed lower rates of ISTH-major bleeding (1.1% vs 2.4%, INSigHT rate vs ARISTOTLE [33] rate, respectively) while results were different for dabigatran according to the dose (1% vs 5.4% for 110 mg die and 6% vs. 5.5% for 150 mg bid, INSigHT vs RELY, respectively) [32].

The differences in some component of the safety and efficacy endpoints between DOACs, albeit statistically significant need to be cautiously interpreted: first, the relatively small sample size and the small number of events during follow-up may have limited the power of the study to detect possible differences between DOACs; second, data resulting from indirect comparison between DOACs may also be explained by possible residual confounders between groups and by play of chance. Moreover, random modification of renal function over time can happen both for non-CKD and CKD patients. Therefore, the present results on comparison between DOACs must be considered as preliminary, exploratory and hypothesis generating.

Real-world data about DOACs' persistence in patients with CKD are still lacking. In the present study, the discontinuation rate in the CKD group was slightly lower than in non-CKD group in terms of treatment interruption (23% vs 18.6% at 2 years), usually due to medical decision to interrupt the anticoagulant treatment in patient at low ischemic risk (es. young males with persistent sinus rhythm after 6 months successful catheter ablation of AF). However, these results are consistent with those reported in the Dresden registry [37] (25.8%) and in the Xantus [38] study (20%). Recently, Vedovati et al. [39] showed a lower discontinuation rate in an Italian cohort; however, in their study the use of reduced dose, which is frequent in our population, was independently associated with treatment interruption. We can hypothesize that the increased treatment interruption in non-CKD patients on dabigatran, and consequent shift to other DOACs, could at first be explained by its decreased gastrointestinal tolerance [40].

Our last consideration concerns the fact that the most recent real-world head to head DOACs comparison are based on insurance or administrative healthcare databases and do not provide accurate information about patient characteristics such as body weight and laboratory tests, including creatinine levels [41]. In fact, if this strategy permits to evaluate high-size cohorts, on the other hand no reliable patient-level information can be obtained to define and analyze well-selected sub-cohorts, such is the case of patients with moderate to severe impaired renal function. A recent registry based on UK Clinical Practice Research Datalink and focused on patients with CKD used an ambiguous definition of renal impairment which was not based laboratory on creatine clearance values [30]. Furthermore, these studies could have an intrinsic risk of misclassification mistakes related to follow-up based on hospital admission codes. For example, all the spectra of thromboembolic events might be underestimated, especially for less serious diagnosis such as transient ischemic attacks. Therefore, the strength of this non-insurance database registry is related to the accurate and extensive data collection available for each patient, and a careful clinical definition of each adverse events during the follow-up.

Limits

The principal limit of this preliminary report is represented by its observational design and the relative small size of the population. Although baseline principal clinical characteristics were comparable among three groups, we cannot exclude some residual confounders unequally represented that could account for the differences arisen among different DOACs. Given the small number of events registered during the follow-up, results have been analyzed only by univariate Cox regression analysis. Finally, being DOACs contraindicated in end-stage chronic renal disease patients on hemodialysis (in the USA only apixaban has been recently approved by FDA), such patients have not been included and still represent a subset of patients in whom the management of anticoagulation remains controversial.

Conclusions

In conclusion, this single tertiary care center real-world, non-insurance database experience shows remarkable safety and efficacy profile of DOACs in patients with non-valvular atrial fibrillation and moderate and severe CKD, with similar thromboembolic and ISTH- major bleeding events compared to those with normal renal function. No differences in all-cause death was evident within different anticoagulant subgroups. Differences arisen after indirect comparison between DOACs are exploratory and must be considered as hypothesis generating and warrant further investigations in larger studies.

Compliance with ethical standards

Conflict of interest All the authors declare that they have no conflict of interest.

Statement of human and animal rights The study was in accordance with the ethical standards of the institutional research committee.

Informed consent All patients provided informed consent for data collection.

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