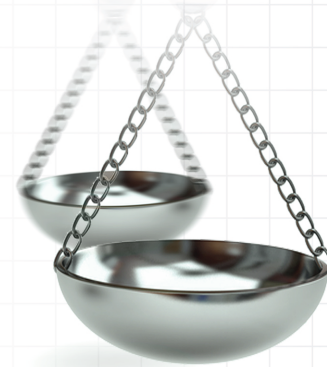




Facing real-life with direct oral anticoagulants in patients with nonvalvular atrial fibrillation: outcomes from the first observational and prospective study in a Spanish population

María Cerdá¹, Juan J Cerezo-Manchado¹, Erik Johansson¹, Fernanda Martínez¹, Mariana Fernández¹, Ana Varela¹, Saray Rodríguez¹, Francesc Bosch¹ & Amparo Santamaría^{*,1}

¹Servicio de Hematología, Hospital Vall d'Hebron, Barcelona, Spain

*Author for correspondence: asantamaria@vhebron.net

Aim: To analyze the effectiveness and safety of direct oral anticoagulants (DOACs) in atrial fibrillation (AF) patients attended in clinical practice. **Methods:** Observational and prospective study of AF patients that started treatment with DOACs. **Results:** 1443 patients (age 77.2 ± 9.7 years, $\text{CHA}_2\text{DS}_2\text{-VASc} = 4.1 \pm 1.5$) were included. 46.0% were taking rivaroxaban, 24.4% dabigatran, 22.5% apixaban and 7.1% edoxaban. Patients taking dabigatran were younger, had lower $\text{CHA}_2\text{DS}_2\text{-VASc}$ and lesser renal insufficiency. Patients taking apixaban had higher $\text{CHA}_2\text{DS}_2\text{-VASc}$ and more renal insufficiency. Rates of stroke/major bleeding/intracranial bleeding were 0.7/1.3/0.2 events/100 patient-years, respectively. **Conclusion:** This was the first prospective study that analyzed the use of all DOACs in AF patients in Spain, showing a good profile in terms of safety and effectiveness in accordance with pivotal studies.

First draft submitted: 18 May 2018; Accepted for publication: 28 November 2018; Published online: 18 January 2019

Keywords: apixaban • atrial fibrillation • clinical practice • dabigatran • edoxaban • rivaroxaban

Atrial fibrillation (AF) is very common in clinical practice, particularly in the elderly segment. Thus, although the overall prevalence of AF is ~1–3% in Europe; this reaches 17% in patients aged 80 years or older [1,2]. Patients with AF are at increased risk of stroke [1]. Cardioembolic stroke in patients with AF is associated with high rates of death (32% within 30 days and 50% within one year of the acute event), disability (approximately 60% among survivors) and recurrence (12% per year) [3–6].

Unless contraindicated, the great majority of AF patients require chronic oral anticoagulation to reduce the risk of stroke, transient ischemic attack and/or systemic embolism [1,7]. Vitamin K antagonists (VKA) have been used for many years for this purpose, with an acceptable efficacy and safety profile but with many limitations that have made it difficult to control, so there is a percentage of patients with AF who are not properly anticoagulated [2,7–9].

In contrast to VKA, direct oral anticoagulants (DOACs) have a predictable anticoagulant effect and do not require periodic monitoring of their anticoagulant effect or continuous dose adjustments [10]. Overall, Phase III clinical trials have shown that, compared with warfarin, it seems that DOACs have at least a similar efficacy for the prevention of thromboembolic complications and a better efficacy in reducing the risk of intracranial hemorrhage and likely all-cause mortality, but higher rates of gastrointestinal bleeding [11,12].

The introduction of DOACs in clinical practice has changed the anticoagulation pattern in AF population. In fact, rates of oral anticoagulation have significantly increased in the last years, particularly due to a higher use of DOACs [13–15]. Observational studies may complete the information reported by clinical trials and may extend the results regarding effectiveness and safety to the overall AF population [16,17]. In this context, observational studies performed with DOACs are of great value. However, the majority of these studies have had a retrospective design, data have come from insurance databases or nationwide/regional registries, clinical characteristics of patients

often have remained unknown, and a comprehensive analysis of data have not been frequently performed [18–20]. Therefore, studies analyzing real-life data about the effectiveness and safety of DOACs in prospective cohorts of AF patients are warranted.

The aim of this study was to analyze the effectiveness and safety of DOACs in a prospective cohort of patients with nonvalvular AF attended in clinical practice in the province of Barcelona, Spain.

Materials & methods

This was an observational and prospective study, in which all patients with nonvalvular AF, with or without prior stroke, attended in the Oral Anticoagulant Treatment Unit of the Hemostasis and Thrombosis Department of the University Hospital Vall d'Hebron from Barcelona (Spain) that had started treatment with any DOAC for the prevention of stroke, were consecutively included. Patients were recruited between January 2015 and September 2017. This study was approved by the Clinical Research Ethics Committee of the hospital. Written informed consent was given by all patients before being included in the study and starting treatment with DOACs. The dosage of the DOACs (dabigatran 150 or 110 mg, rivaroxaban 20 or 15 mg, apixaban 5 or 2.5 mg and edoxaban 60 or 30 mg) was prescribed according to the clinical criteria of the physicians that attended the patients in the Oral Anticoagulant Treatment Unit of the Hospital Vall d' Hebron.

All patients were followed-up every 3 months during the first year of treatment with DOACs and then every 6 months, except in those patients with more comorbidities or complexity that were attended every 3 months according to the clinical criteria of the physicians. Patients were followed up until discontinuation of DOACs or the last visit performed. No study-specific diagnostic or therapeutic intervention was performed.

Clinical data were collected from the medical history of the patients and during physician interview at baseline and follow-up visits. Data were recorded by the investigators in a case report form specifically designed for this study. Biodemographic data (age, sex), cardiovascular risk factors (hypertension, diabetes), vascular disease (heart failure, prior stroke or transient ischemic attack) and renal function estimated by the Cockcroft–Gault formula were recorded [21]. The thromboembolic risk was estimated with the CHA₂DS₂-VASc scale [22]. The appropriateness of dosage of DOACs according to the clinical profile of patients was analyzed. Thromboembolic outcomes (ischemic stroke) and bleeding events (major bleeding or intracranial hemorrhage) during treatment with DOACs were recorded. Major bleeding was defined according to 2005 ISTH (International Society on Thrombosis and Haemostasis bleeding scale) criteria [23]. According to this definition, major bleeding included fatal bleeding, and/or symptomatic bleeding in a critical area or organ (i.e., intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome), and/or bleeding causing a fall in hemoglobin level of ≥ 2 g/dl, or leading to transfusion of ≥ 2 units of whole blood or red cells [23].

Statistical analysis

For the descriptive analysis, quantitative variables were described with measures of central tendency and dispersion (mean and standard deviation) and qualitative variables were described as absolute (n) and relative (%) frequencies. When two means were compared, the Student's t-test or the Mann–Whitney U test were used, as appropriate. When more than two means were compared, the ANOVA test or the Kruskal–Wallis test were performed, as appropriate. Categorical variables were compared with the χ^2 test or the Fisher exact test when appropriate. A multivariate analysis was performed to assess those factors associated with the risk of stroke and bleeding. Thromboembolic and bleeding events during treatment with DOACs were calculated as events per 100 patient-years. A log-rank test was performed to identify whether rates of outcomes (stroke, major bleeding and intracranial bleeding) differed according to the type of DOACs. All patients who took at least one dose of DOACs were included for this analysis (intention-to-treat population). Statistical significance was set at a p-value < 0.05. The statistical analysis was performed using SPSS 21.0 (SPSS Inc., IL, USA).

Results

Between January 2015 and September 2017, a total of 1443 patients were included in the study. Mean age was 77.2 ± 9.7 years, 52.8% of patients were women, 20.0% of patients had prior stroke or transient ischemic attack, 34.4% a creatinine clearance < 50 ml/min and mean CHA₂DS₂-VASc was 4.1 ± 1.5 . A total of 663 (46.0%) patients were taking rivaroxaban, 352 (24.4%) dabigatran, 325 (22.5%) apixaban and 103 (7.1%) edoxaban. During the follow-up, only five patients (0.3%) switched from one DOAC to another DOAC (one patient from edoxaban 30 mg to apixaban 2.5 mg; one patient from edoxaban 60 mg to apixaban 5 mg; one patient from

rivaroxaban 20 mg to dabigatran 150 mg; one patient from dabigatran 110 mg to apixaban 2.5 mg; and one patient from apixaban 5 mg to dabigatran 110 mg). When compared among patients taking different DOACs, patients taking dabigatran were younger (mean age 73.1 ± 15.2 years), had a lower CHA₂DS₂-VASc score (3.9 ± 1.5) and lesser diabetes (25.6%), renal insufficiency (18.8%) and heart failure (10.8%). By contrast, patients taking apixaban had a higher CHA₂DS₂-VASc score (4.4 ± 1.5) and more renal insufficiency (54.5%). No significant differences were found regarding the history of stroke or transient ischemic attack according to the type of DOAC (Table 1).

A total of 804 (55.7%) patients were taking the standard dose of DOACs and 639 (44.3%) the low dose. Compared with patients taking the standard dose of DOACs, patients taking the low doses of DOACs were older (75.9 ± 9.7 vs 79.3 ± 9.4 ; $p < 0.001$), had a higher CHA₂DS₂-VASc score (3.9 ± 1.5 vs 4.3 ± 1.5 , $p < 0.001$) and more hypertension, renal insufficiency and heart failure (Table 1).

Baseline clinical characteristics of the study population according to the dose of DOACs were shown in Table 2. The proportion of patients taking the low dose of each DOAC was as follows: 82.1% with dabigatran 110 mg, 24.9% with rivaroxaban 15 mg, 50.8% apixaban 2.5 mg and 19.4% edoxaban 30 mg. In all cases, when compared with patients taking the standard dose of DOACs, those patients taking the low dose of DOACs were older and had a worse renal function. CHA₂DS₂-VASc score was higher with low doses of DOACs in the case of rivaroxaban (3.9 ± 1.4 vs 4.3 ± 1.3 ; $p = 0.001$) and apixaban (3.9 ± 1.5 vs 4.9 ± 1.4 ; $p < 0.001$), without significant differences among patients taking dabigatran or edoxaban. Prior stroke or transient ischemic attack was more common in patients taking dabigatran 150 mg (36.5%).

The appropriateness of the prescription of DOACs according to the summary of product characteristics was analyzed. With regard to the standard doses, 16.8, 15.0, 6.3 and 6.0% of patients treated with rivaroxaban 20 mg, apixaban 5 mg, dabigatran 150 mg and edoxaban 60 mg, respectively, did not receive the suitable dosage. With respect to the low doses, the proportion of patients with an inadequate dosage according to the summary of product characteristics was 12.1% for rivaroxaban 15 mg, 28.5% for apixaban 2.5 mg, 48.1% for dabigatran 110 mg and 0% for edoxaban 30 mg. Of note, since bodyweight was not recorded, it is likely that the proportion of patients with a suitable dosage may be lower than those reported in the case of apixaban and edoxaban.

Overall, mean follow-up was 1.7 ± 1.1 years (1.5 ± 1.0 years for standard doses, 1.8 ± 1.3 years for low doses, 2.5 ± 1.4 years for dabigatran, 1.6 ± 1.0 years for rivaroxaban, 1.3 ± 0.7 years for apixaban and 0.8 ± 0.4 years for edoxaban).

Rates of ischemic stroke, major bleeding and intracranial bleeding were 0.7, 1.3 and 0.2 events per 100 patient-years, respectively (Table 3). Major bleeding had more commonly a gastrointestinal origin (60%), followed by the urinary tract (20%) and soft tissues (20%). The risk was higher among patients taking dabigatran 110 mg (82.3%). There were only four patients with intracranial hemorrhage, two with dabigatran and two with apixaban (0.15 events per 100 patient-years).

When compared between different DOACs, although rates of ischemic stroke were higher with edoxaban, this difference did not reach statistical significance ($p = 0.561$ in the log-rank test), but the small number of patients and the low follow-up should be considered. By contrast, rates of major bleeding were higher with dabigatran (1.8 events per 100 patient-years) and apixaban (1.7 events per 100 patient-years) and lower with rivaroxaban (0.8 events per 100 patient-years; $p = 0.04$ rivaroxaban vs the other DOACs in the log-rank test; Table 3).

No significant differences were found regarding rates of thromboembolic events and intracranial hemorrhage according to the dose of DOACs (standard vs low doses). However, rates of major bleeding were higher among those patients taking the low dose of DOACs vs the standard dose (1.9 vs 0.9 events per 100 patient-years; $p = 0.008$; Table 3). Rates of ischemic stroke with edoxaban were more common with the low doses when compared with the standard doses (12.5 vs 0 events per 100 patient-years, respectively; $p = 0.02$), taking into account that the data, in the case of edoxaban, were not comparable. No other differences were found according to the dose of each type of DOAC (Table 4).

In the multivariate analysis, prior stroke (hazard ratio [HR]: 4.83; 95% confidence interval [CI]: 1.449–16.071; $p = 0.01$) and low doses of edoxaban (HR: 19.52; 95% CI: 1.71–222.88; $p = 0.017$) were independently associated with an increased risk of stroke. With regard to the risk of bleeding, rivaroxaban was associated with a lesser bleeding risk (HR: 0.59; 95% CI: 0.36–0.96; $p = 0.035$), but dabigatran with a higher bleeding risk (HR: 2.01; 95% CI: 1.25–3.25; $p = 0.004$). Similarly, low doses of rivaroxaban were associated with a lesser risk of bleeding (HR: 0.23; 95% CI: 0.07–0.76; $p = 0.015$) and low doses of dabigatran showed a trend toward a higher bleeding risk (HR: 1.89; 95% CI: 0.99–3.64; $p = 0.055$).

Table 1. Baseline clinical characteristics of the study population according to the type and dose of direct oral anticoagulants.

	Type of DOACs				Dose of DOACs		
	Total (n = 1443)	Rivaroxaban (n = 663)	Apixaban (n = 325)	Dabigatran (n = 352)	Edoxaban (n = 103)	P _{DOACs}	
Age (years)	77.2 ± 9.7	77.8 ± 9.7	78.9 ± 8.7	73.1 ± 15.2	78.7 ± 7.0	<0.001	Low dose (n = 639; 44.3%)
Sex: women, n (%)	762 (52.8)	364 (54.9)	157 (48.3)	193 (54.8)	48 (46.6)	NS	Standard dose (n = 804; 55.7%)
CHA ₂ D ₅ -VAScc	4.1 ± 1.5	4.0 ± 1.4	4.4 ± 1.5	3.9 ± 1.5	4.2 ± 1.5	<0.001	75.9 ± 9.7
Hypertension, n (%)	1226 (84.9)	564 (85.1)	275 (84.6)	299 (84.9)	88 (85.4)	NS	420 (52.2)
Diabetes, n (%)	431 (29.9)	173 (26.1)	129 (39.7)	90 (25.6)	39 (37.9)	<0.001	3.9 ± 1.5
CrCl (ml/min)	59.0 ± 21.3	59.1 ± 19.8	49.8 ± 21.5	66.4 ± 21.7	62.3 ± 18.0	<0.001	669 (83.2)
CrCl < 50 ml/min, n (%)	497 (34.4)	229 (34.5)	177 (54.5)	66 (18.8)	25 (24.3)	<0.001	236 (29.3)
Heart failure, n (%)	264 (18.3)	99 (14.9)	95 (29.2)	38 (10.8)	32 (31.1)	<0.001	65.1 ± 18.5
Prior stroke/TIA, n (%)	289 (20.0)	123 (18.6)	81 (24.9)	68 (19.3)	17 (16.5)	NS	130 (16.2)
DOAC: Direct oral anticoagulant; CrCl: Creatinine clearance; NS: Not significant; TIA: Transient ischemic attack.							367 (57.4)
							126 (15.7)
							170 (21.1)
							138 (21.6)
							119 (18.6)
							0.03
							NS

Table 2. Baseline clinical characteristics of the study population according to the dose of each type of direct oral anticoagulant.

	Rivaroxaban 20 mg (n = 498; 75.1%)	Rivaroxaban 15 mg (n = 165; 24.9%)	P _{Rivaroxaban}	Apixaban 5 mg (n = 160;49.2%)	Apixaban 2.5 mg (n = 165; 50.8%)	P _{Apixaban}	Dabigatran 150 mg (n = 63; 17.9%)	Dabigatran 110 mg (n = 289; 82.1%)	P _{Dabigatran}	Edoxaban 60 mg (83; 80.6%)	Edoxaban 30 mg (n = 20;19.4%)	P _{Edoxaban}
Age (years)	76.6 ± 9.8	81.4 ± 8.3	<0.001	75.0 ± 9.3	82.7 ± 5.9	<0.001	69.2 ± 9.9	73.9 ± 16.0	0.02	78.0 ± 7.1	81.8 ± 5.8	0.02
Sex, women, n (%)	278 (55.8)	86 (52.1)	NS	65 (40.6)	92 (55.8)	0.006	34 (54.0)	159 (55.0)	NS	43 (51.8)	5 (25.0)	0.03
CHA ₂ D ₂ -VASc	3.9 ± 1.4	4.3 ± 1.3	0.001	3.9 ± 1.5	4.9 ± 1.4	<0.001	3.7 ± 1.7	3.9 ± 1.5	NS	4.1 ± 1.5	4.6 ± 1.3	NS
Hypertension, n (%)	420 (84.3)	144 (87.3)	NS	125 (78.1)	150 (90.9)	0.001	52 (82.5)	247 (85.5)	NS	72 (86.7)	16 (80.0)	NS
Diabetes, n (%)	121 (24.3)	52 (31.5)	NS	66 (41.3)	63 (38.2)	NS	21 (33.3)	69 (23.9)	NS	28 (33.7)	11 (55.0)	NS
CrCl (ml/min)	64.4 ± 18.5	43.0 ± 14.1	<0.001	62.8 ± 18.3	37.2 ± 16.2	<0.001	73.4 ± 19.5	64.8 ± 21.9	0.004	68.1 ± 14.8	38.3 ± 6.7	<0.001
CrCl < 50 ml/min, n (%)	84 (16.8)	145 (87.9)	<0.001	40 (25.0)	137 (83.0)	<0.001	1 (1.6)	65 (22.5)	<0.001	5 (6.0%)	20 (100)	<0.001
Heart failure, n (%)	62 (12.5)	37 (22.4)	0.001	32 (20.0)	63 (38.2)	<0.001	6 (9.5)	32 (11.1)	NS	26 (31.3)	6 (30.0)	NS
Prior stroke/TIA, n (%)	96 (19.3)	27 (16.4)	NS	39 (24.4)	42 (25.5)	NS	23 (36.5)	45 (15.6)	<0.001	12 (14.5)	5 (25.0)	NS

DOAC: Direct oral anticoagulant; CrCl: Creatinine clearance; NS: Not significant; TIA: Transient ischemic attack.

Table 3. Thromboembolic and bleeding events according to the type and dose of direct oral anticoagulants.

	Type of DOACs				Dose of DOACs		
	Total (n = 1443)	Rivaroxaban (n = 663)	Apixaban (n = 325)	Dabigatran (n = 352)	Edoxaban (n = 103)	Standard dose (n = 804; 55.7 %)	Low dose (n = 639; 44.3 %)
Ischemic stroke							
n (%)	16 (1.1)	5 (0.7)	4 (1.2)	5 (1.4)	2 (1.9)	6 (0.7)	10 (1.6)
Events/100 patient-years	0.7	0.5	0.9	0.6	2.4	0.5	0.9
Major bleeding							
n (%)	33 (2.3)	9 (1.3)	7 (2.2)	16 (4.5)	1 (1.0)	11 (1.4)	22 (3.4)
Events/100 patient-years	1.3	0.8	1.7	1.8	1.2	0.9	1.9
Intracranial hemorrhage							
n (%)	4 (0.3)	0	2 (0.6)	2 (0.6)	0	0 (0)	4 (0.6)
Events/100 patient-years	0.2	0	0.5	0.2	0	0	0.3
DOAC: Direct oral anticoagulant; NS: Not significant.							

Table 4. Thromboembolic and bleeding events according to the dose of each type of direct oral anticoagulant.

	Rivaroxaban 20 mg (n = 498; 75.1%)	Rivaroxaban 15 mg (n = 165; 24.9%)	P _{Rivaroxaban}	Apixaban 5 mg (n = 160; 49.2%)	Apixaban 2.5 mg (n = 165; 50.8%)	P _{Apixaban}	Dabigatran 150 mg (n = 63; 17.9%)	Dabigatran 110 mg (n = 289; 82.1%)	P _{Dabigatran}	Edoxaban 60 mg (83; 80.6%)	Edoxaban 30 mg (n = 20; 19.4%)	P _{Edoxaban}
Ischemic stroke												
n (%)	4 (0.8)	1 (0.6)	NS	1 (0.6)	3 (1.8)	NS	1 (1.6)	4 (1.4)	NS	0	2 (10.0)	0.02
Events/100 patient-years	0.5	0.4		0.5	1.4		0.6	0.6		0	12.5	
Major bleeding												
n (%)	7 (1.4)	2 (1.2)	NS	2 (1.2)	5 (3.0)	NS	1 (1.6)	15 (5.2)	NS	1 (1.2)	0	NS
Events/100 patient-years	0.9	0.8		1.0	2.3		0.6	2.1		1.5	0	
Intracranial hemorrhage												
n (%)	0	0	NS	0	2 (1.2)	NS	0	2 (0.7)	NS	0	0	NS
Events/100 patient-years	0	0		0	0.9		0	0.3		0	0	
DOAC: Direct oral anticoagulant; NS: Not significant.												

The clinical characteristics, appropriateness of dosage and outcomes were also analyzed among patients at very high risk of stroke ($\text{CHA}_2\text{DS}_2\text{-VASc} > 2$). Despite patients were older and the thromboembolic risk higher, the appropriateness of dose and stroke and major bleeding rates were similar to those of the overall study population (Table 5).

Discussion

This is the first observational and prospective study performed in a wide cohort of real-life patients with nonvalvular AF treated with the four DOACs currently marketed (dabigatran, rivaroxaban, apixaban and edoxaban) in Spain. Of note, this was an independent study, since it was not supported by the industry. In the last years, the prescription of DOACs has markedly increased and even in some countries these agents have now surpassed VKAs as the anticoagulant of choice [24]. In our study, rivaroxaban was the DOAC more commonly prescribed (46.0% of all prescriptions), followed by dabigatran, apixaban and edoxaban. This pattern of prescription was similar to that found in other studies [25]. It is likely that the once daily dose of rivaroxaban as well as its simplicity for dose adjustment may explain, at least in part, these numbers. On the other hand, since edoxaban is the last DOAC marketed, not much information about the use of this drug in clinical practice is currently available [26]. In this context, our study may provide a comprehensive view about the use of the four DOACs in clinical practice.

Due to the ageing of the population as well as the higher prevalence of some chronic conditions, such as hypertension, diabetes or cardiovascular disease, the clinical profile of patients with nonvalvular AF has changed in the last few years [2,27,28]. As a result, nowadays, nonvalvular AF patients are old, have many comorbidities and are frequently polymedicated. In our study, mean age was 77.2 years, nearly 53% of patients were women, mean $\text{CHA}_2\text{DS}_2\text{-VASc}$ was 4.1, 20% of patients had prior stroke or transient ischemic attack, and approximately one third had a creatinine clearance <50 ml/min. These figures were in line with recent publications that have analyzed the clinical profile of patients taking DOACs in routine practice [27,28]. As a result, due to the complexity of current patients with nonvalvular AF, DOACs seem a better choice than VKA in order to assure a more effective and safer anticoagulation.[1]

When we compared the clinical profile of patients included in our study, with that of the pivotal clinical trials [29–32], our patients were older and a high proportion of women were included, regardless the type of DOAC. The proportion of patients with stroke or transient ischemic attack included in the RE-LY trial was approximately 20%, 55% in the ROCKET-AF trial, 19% in the ARISTOTLE trial and 28% in the ENGAGE AF-TIMI 48 trial [29–32]. In our study, these numbers were approximately 19% for dabigatran and rivaroxaban, 25% for apixaban and 17% for edoxaban. In RE-LY, approximately 19% of patients had a creatinine clearance <50 ml/min, 21% in ROCKET-AF, 17% in ARISTOTLE and 20% in ENGAGE AF-TIMI 48 [29–32]. These figures in our study were approximately 19, 35, 55 and 24%, respectively. All these data indicate that there were relevant differences in the clinical profile among patients included in the pivotal clinical trials with DOACs and the counterparts recruited in our study. As a result, these numbers strongly suggest that the data regarding the efficacy and safety of clinical trials cannot be directly translated into clinical practice and that the observational and prospective studies are required to assess these issues in routine practice.

In our study, when we compared patients taking different DOACs, patients taking dabigatran were younger, had a lower $\text{CHA}_2\text{DS}_2\text{-VASc}$ score and lesser renal insufficiency. By contrast, patients taking apixaban had a higher $\text{CHA}_2\text{DS}_2\text{-VASc}$ score and more renal insufficiency. A similar pattern of prescription has been recently reported by other authors. Thus, a study performed using the Danish nationwide registry data showed that among AF patients initiating treatment with DOACs or VKA, those patients who were initiated on apixaban had a higher $\text{CHA}_2\text{DS}_2\text{-VASc}$ score than patients initiated on VKAs and the opposite results were found with dabigatran [33]. It is likely that the different clinical profile of patients found in our study according to the type of DOAC (i.e., 54% of apixaban users and only 19% of dabigatran users had a creatinine clearance <50 ml/min) may be related with the fact that many physicians may be prescribing these medications based at least in part on clearance mechanism. Importantly, since the characteristics of patients initiated on DOACs have changed over time, new studies comparing DOACs versus VKA may be warranted [24].

In our study, the clinical characteristics of patients were analyzed according to the dose of DOACs. Patients taking the low doses of DOACs were older and had a worse renal function when compared with patients taking the standard doses. Due to the design of the RE-LY trial, patients equally took dabigatran 150 and 110 mg [29]. In ROCKET-AF, 21% of patients took 15 mg of rivaroxaban and the remaining 79% rivaroxaban 20 mg [30]. In the ARISTOTLE trial, only 4.7% of patients took apixaban 2.5 mg and the rest of patients 5 mg twice daily [31]. In

Table 5. Clinical characteristics and outcomes according to the dose of each type of direct oral anticoagulant among patients with CHA ₂ DS ₂ -VASC > 2.										
	Rivaroxaban 20 mg (n = 418)	Rivaroxaban 15 mg (n = 152)	P _{Rivaroxaban}	Apixaban 5 mg (n = 132)	Apixaban 2.5 mg (n = 160)	P _{Apixaban}	Dabigatran 150 mg (n = 47)	Dabigatran 110 mg (n = 239)	P _{Dabigatran}	P _{Edoxaban}
Mean age (years)	78.6 ± 8.0	82.2 ± 7.2	<0.001	77.2 ± 8.1	83.0 ± 5.8	<0.001	72.7 ± 7.3	78.2 ± 9.1	0.0001	0.03
CHA ₂ DS ₂ -Vasc	4.3 ± 1.1	4.6 ± 1.1	0.004	4.4 ± 1.3	5.0 ± 1.3	0.0001	4.5 ± 1.3	4.4 ± 1.1	NS	NS
Inappropriate dosage, n (%)	82 (19.6)	14 (9.2)	0.003	19 (14.4)	42 (26.3)	0.01	4 (8.5)	106 (44.4)	<0.001	NS
Ischemic stroke										
n (%)	4 (1.0)	1 (0.7)	NS	1 (0.8)	3 (1.9)	NS	1 (2.1)	4 (1.7)	NS	0.03
Events/100 patient-years	0.6	0.4	NS	0.6	1.5		0.8	0.7		13.1
Major bleeding										
n (%)	5 (1.2)	2 (1.3)	NS	1 (0.8)	4 (2.5)	NS	1 (2.1)	12 (5.0)	NS	0
Events/100 patient-years	0.8	0.8		0.6	1.9		0.8	2.0		1.8
DOAC: Direct oral anticoagulant; NS: Not significant.										

ENGAGE AF-TIMI 48, after randomization, dose reductions occurred in 7.1% of the patients, and dose increases in 1.2% [32]. In our study, approximately 82% of patients were taking dabigatran 110 mg, 25% rivaroxaban 15 mg, 51% apixaban 2.5 mg and 19% edoxaban 30 mg. According to the summary of product characteristics of DOACs, the proportion of patients with an unsuitable dosage ranged from 6–17% in the case of standard doses, and from 0% to 48% in the case of low doses. These numbers did not significantly change among patients at higher risk of stroke (6–20 and 0–44%, respectively). Of note, these numbers could be higher in the case of apixaban and edoxaban, since data regarding bodyweight were not recorded. Despite that, our data strongly suggest that in a significant proportion of patients, DOACs may be prescribed inadequately. Since the number of events was low in our cohort of patients, the impact of inappropriate dosage prescription on outcomes could not be determined properly. Remarkably, in our study, in contrast to expected, CHA₂DS₂-VASc score was higher (greater thromboembolic risk) in those patients taking the low doses of rivaroxaban and apixaban when compared with their counterparts. Previous studies have shown that although inappropriate drug use is more common with VKA than with DOACs, this also frequently occurs with DOACs, particularly with the twice daily regimens [34–37]. This is very relevant, since using inadequately the low-dose regimens of DOACs is associated with a lesser effectiveness in routine practice and consequently, with a higher risk of stroke [20,38,39].

In our study, overall mean follow-up was 1.7 years (longer with dabigatran and shorter with edoxaban, as expected according to the dates in which these drugs were marketed). Importantly, to date, this is the ‘real-life’ study with the longest follow-up of patients taking the four DOACs.

Overall, rates of ischemic stroke, major bleeding and intracranial bleeding were 0.7, 1.3 and 0.2 events per 100 patient-years, respectively. Remarkably, rates of ischemic stroke and intracranial hemorrhage were similar among different DOACs, but rates of major bleeding were higher with dabigatran and apixaban and lower with rivaroxaban. A worse clinical profile, with more renal insufficiency, could explain, at least in part, the higher rates of major bleeding found with apixaban.

In the pivotal clinical trials with DOACs, the annual rates of stroke/systemic embolism ranged from 0.9 to 2.3% and the annual rates of major bleeding from 2.1 to 3.6% [29–32]. With regard to real-life studies, in the Dresden NOAC Registry, an ongoing, prospective and non-interventional registry of patients on treatment with DOACs in daily care, among patients taking dabigatran, rates of the combined end point of stroke/transient ischemic attack/systemic embolism and major bleeding were 1.9/100 and 2.3/100 patient-years, respectively, in the on-treatment analysis [40]. Among patients taking rivaroxaban, these figures were 1.7/100 and 3.0/100 patient-years, respectively [41], and among patients taking apixaban, 1.8/100 and 2.8/100 patient-years, respectively [42]. In our study, annual rates of ischemic stroke and major bleeding were 0.7 and 1.3%, respectively. Differences in the definitions of outcomes, in the clinical profile of patients included and considering that our study was unicenter, assuring a better homogeneity in the management of patients treated with DOACs, may explain the disparities found in the rates of thromboembolic and bleeding events between studies.

In our study, major bleeding occurred more commonly in the gastrointestinal tract. However, whereas in our study this was more frequent with dabigatran 110 mg, other studies have found a higher risk with rivaroxaban. By contrast, a recent systematic review and network meta-analysis showed no differences between DOACs [43–45].

This study has some limitations. Due to the observational and prospective design of the study, no control group was available and bias could not be controlled. As a result, comparisons between groups must be taken with caution. However, this design is the best to investigate the use of drugs in clinical practice. Since this study only included patients attended in the Hematology and Thrombosis Unit of the University Hospital Vall d’Hebron from Barcelona, the results can only be applied to patients with a similar clinical profile and healthcare system. However, since all patients were attended in the same center, this may assure a high homogeneity in the management of this population. Since only 103 patients taking edoxaban were included, this may limit the generalization of the results. However, this study is one of the first studies that have published some information about the use of edoxaban in routine practice. Finally, only 5 patients (0.3%) switched from one DOAC to another DOAC during the study, but this did not have a relevant impact on the results.

Conclusion

This is the first study that has analyzed in a wide prospective cohort of nonvalvular AF patients the use of the four DOACs in clinical practice in Spain. In addition, to date, this is the study with the longest follow-up of patients taking the four DOACs in routine practice. Patients were old and mean CHA₂DS₂-VASc was 4.1. According to the summary of product characteristics of DOACs, the proportion of patients with unsuitable dosage ranged from 6 to

17% in the case of standard doses, and from 0 to 48% in the case of low doses, despite being treated in a specialized center. After a mean follow-up of 1.7 years, rates of ischemic stroke, major bleeding and intracranial bleeding were 0.7, 1.3 and 0.2 events per 100 patient-years, respectively. Although rates of major bleeding were higher with dabigatran and apixaban and lower with rivaroxaban, overall, the rates of ischemic stroke and intracranial bleeding were similar between different DOACs. Despite differences in the clinical profile, this study showed in a 'real-life' cohort of patients with AF, that the use of DOACs in clinical practice was effective and safe. Due to the characteristics of our study (i.e., prospective design, independent, wide sample of patients, long follow-up, etc.), our data may be applied to the majority of patients with nonvalvular AF in clinical practice.

Summary points

- Studies analyzing real-life data about the effectiveness and safety of direct oral anticoagulants (DOACs) in prospective cohorts of atrial fibrillation (AF) patients are warranted.
- The objective of this study was to analyze the effectiveness and safety of DOACs in a prospective cohort of AF patients attended in clinical practice.

Methods

- This was an observational and prospective study, in which patients with nonvalvular AF attended in the Oral Anticoagulant Treatment Unit of the Hospital Vall d'Hebron (Barcelona, Spain) that had started treatment with any of the four DOACs (dabigatran, rivaroxaban, apixaban and edoxaban) were consecutively included.

Results

- A total of 1443 patients (mean age 77.2 ± 9.7 years, 52.8% women, $\text{CHA}_2\text{DS}_2\text{-VASc}$ 4.1 ± 1.5) were included.
- A total of 46.0% of patients were taking rivaroxaban, 24.4% dabigatran, 22.5% apixaban and 7.1% edoxaban.
- The proportion of patients with unsuitable dosage ranged from 6 to 17% in the case of standard doses, and from 0 to 48% in the case of low doses.
- After a mean follow-up of 1.7 ± 1.1 years, rates of ischemic stroke, major bleeding and intracranial bleeding were 0.7, 1.3 and 0.2 events per 100 patient-years, respectively.
- Although rates of major bleeding were higher with dabigatran and apixaban and lower with rivaroxaban, the rates of ischemic stroke and intracranial bleeding were similar between different DOACs.

Conclusion

- To date, this is the first prospective study that has analyzed the management and outcomes with the four DOACs currently marketed in AF patients in Spain.
- This study showed in a 'real-life' cohort of patients with AF, that the use of DOACs in clinical practice was effective and safe.

Author contributions

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. Conception/design: M Cerdá, E Johansson, A Santamaría. Collection and/or assembly of data: M Cerdá, M Fernández, E Johansson, F Martínez, S Rodríguez, A Santamaría, A Varela. Data analysis and interpretation: M Cerdá, JJ Cerezo-Manchado, E Johansson. Manuscript writing: M Cerdá, JJ Cerezo-Manchado, A Santamaría. Final approval of manuscript: F Bosch, M Cerdá, A Santamaría.

Acknowledgment

The authors want to thank the Medicine Department of the Autonomous University of Barcelona for the scientific support to the realization of this study.

Financial & competing interests disclosure

M Cerdá has received financial support from Bayer, Daiichi Sankyo, Boehringer Ingelheim and Sanofi for various scientific activities. E Johansson has received financial support from Bayer and Daiichi Sankyo for various scientific activities. F Martínez has received financial support from Bayer and Daiichi Sankyo for various scientific activities. M Fernández has received financial support from Bayer. F Bosch has received honoraria and research grants from Roche, Celgene, Takeda, Astra Zeneca, Novartis, Abbvie and Janssen. A Santamaría has participated in Advisory Boards for Octapharma, Novo Nordisk, Bayer, Pfizer, BMS, Sobi, Shire, Roche, Sanofi, LEO Pharma, Rovi, Daiichi Sankyo, Werfen and Ferrer. A Santamaría has received travel support from Octapharma, Novo Nordisk, Bayer, Pfizer, BMS, Sobi, Bayer, Shire, Roche, Sanofi, LEO Pharma, Rovi, Daiichi Sankyo and Werfen. A Santamaría has received Research Support: Rovi, Shire, Bayer, LEO Pharma, BMS, Pfizer. A Santamaría has done consultancy for Bayer, Pfizer,

BMS and Rovi. A Santamaría has received honoraria per conferences from Octapharma, Novo Nordisk, Bayer, Pfizer, BMS, Sobi, Shire, Sanofi, LEO Pharma, Rovi, Daiichi Sankyo, Werfen and Ferrer. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Editorial assistance was provided by Content Ed Net (Madrid, Spain) and funded by the authors.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

References

Papers of special note have been highlighted as: • of interest

- Kirchhof P, Benussi S, Kotecha D *et al.* 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur. Heart J.* 37(38), 2893–2962 (2016).
- Barrios V, Calderón A, Escobar C, de la Figuera M. Patients with atrial fibrillation in a primary care setting: Val-FAAP study. *Rev. Esp. Cardiol. (Engl. Ed.)* 65(1), 47–53 (2012).
- Masjuán J, Álvarez-Sabín J, Blanco M *et al.* Current management of antithrombotic treatment in patients with non valvular atrial fibrillation and prior history of stroke or transient ischemic attack. *Rev. Neurol.* 59(1), 25–36 (2014).
- Marini C, De Santis F, Sacco S *et al.* Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. *Stroke* 36(6), 1115–1119 (2005).
- Gladstone DJ, Bui E, Fang J *et al.* Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated. *Stroke* 40(1), 235–240 (2009).
- Hart RG, Sherman DG, Easton JD, Cairns JA. Prevention of stroke in patients with nonvalvular atrial fibrillation. *Neurology* 51(3), 674–681 (1998).
- Barrios V, Escobar C, Calderón A, Rodríguez Roca GC, Llisteri JL, Polo García J. Use of antithrombotic therapy according to CHA2DS2-VASc score in patients with atrial fibrillation in primary care. *Rev. Esp. Cardiol. (Engl. Ed.)* 67(2), 150–151 (2014).
- Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann. Intern. Med.* 146(12), 857–867 (2007).
- Hsu JC, Freeman JV. Underuse of vitamin K antagonist and direct oral anticoagulants for stroke prevention in patients with atrial fibrillation: a contemporary review. *Clin. Pharmacol. Ther.* 104(2), 301–310 (2018).
- Franco Moreno AI, Martín Díaz RM, García Navarro MJ. Direct oral anticoagulants: an update. *Med. Clin. (Barc.)* 151(5), 198–206 (2018).
- López-López JA, Sterne JAC, Thom HHZ *et al.* Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. *BMJ* 359, j5058 (2017).
- Ruff CT, Giugliano RP, Braunwald E *et al.* Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 383(9921), 955–962 (2014).
- **This meta-analysis showed that direct oral anticoagulants (DOACs) have a better benefit–risk profile than vitamin K antagonists.**
- Marzec LN, Wang J, Shah ND *et al.* Influence of direct oral anticoagulants on rates of oral anticoagulation for atrial fibrillation. *J. Am. Coll. Cardiol.* 69(20), 2475–2484 (2017).
- **Shows that the introduction of DOACs in routine practice has increased overall anticoagulation rates.**
- Yu AYY, Malo S, Svenson LW, Wilton SB, Hill MD. Temporal trends in the use and comparative effectiveness of direct oral anticoagulant agents versus warfarin for nonvalvular atrial fibrillation: a Canadian population-based study. *J. Am. Heart Assoc.* 6(11), pii: e007129 (2017).
- Alalwan AA, Voils SA, Hartzema AG. Trends in utilization of warfarin and direct oral anticoagulants in older adult patients with atrial fibrillation. *Am. J. Health Syst. Pharm.* 74(16), 1237–1244 (2017).
- Barón-Esquivias G, Marín F, Sanmartín Fernández M. Rivaroxaban in patients with atrial fibrillation: from ROCKET AF to everyday practice. *Expert Rev. Cardiovasc. Ther.* 15(5), 403–413 (2017).
- Russo V, Rago A, Proietti R *et al.* Efficacy and safety of the target-specific oral anticoagulants for stroke prevention in atrial fibrillation: the real-life evidence. *Ther. Adv. Drug Saf.* 8(2), 67–75 (2017).
- Proietti M, Romanazzi I, Romiti GF, Farcomeni A, Lip GYH. Real-world use of apixaban for stroke prevention in atrial fibrillation: a systematic review and meta-analysis. *Stroke* 49(1), 98–106 (2018).

19. Ntaios G, Papavasileiou V, Makaritsis K, Vemmos K, Michel P, Lip GYH. Real-world setting comparison of nonvitamin K antagonist oral anticoagulants versus vitamin K antagonists for stroke prevention in atrial fibrillation: a systematic review and meta-analysis. *Stroke* 48(9), 2494–2503 (2017).
20. Escobar C, Martí-Almor J, Pérez Cabeza A, Martínez Zapata MJ. Direct oral anticoagulants versus vitamin K antagonists in patients with atrial fibrillation: a systematic review and meta-analysis. *Rev. Esp. Cardiol.* DOI: 10.1016/j.rec.2018.03.009 (2018), (Epub ahead of print)
- **This meta-analysis of real-life studies showed that in routine practice, compared with warfarin, DOACs exhibited some differences on outcomes, particularly when low doses were used.**
21. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am. J. Kidney. Dis.* 39(2 Suppl. 1), S1–S266 (2002).
22. Lip GY, Nieuwlaar R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 137(2), 263–272 (2010).
23. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antithrombotic medicinal products in non-surgical patients. *J. Thromb. Haemost.* 3(4), 692–694 (2005).
24. Loo SY, Dell’Aniello S, Huiart L, Renoux C. Trends in the prescription of novel oral anticoagulants in UK primary care. *Br. J. Clin. Pharmacol.* 83(9), 2096–2106 (2017).
25. Lee SR, Choi EK, Han KD, Cha MJ, Oh S, Lip GYH. Temporal trends of antithrombotic therapy for stroke prevention in Korean patients with non-valvular atrial fibrillation in the era of non-vitamin K antagonist oral anticoagulants: a nationwide population-based study. *PLoS ONE* 12(12), e0189495 (2017).
26. Pottegård A, Grove EL, Hellfritsch M. Use of direct oral anticoagulants in the first year after market entry of edoxaban: a Danish nationwide drug utilization study. *Pharmacoepidemiol. Drug. Saf.* 27(2), 174–181 (2018).
27. de la Figuera M, Cinza S, Marín N, Egocheaga I, Prieto MA. Clinical characteristics of patients with atrial fibrillation treated with direct oral anticoagulants attended in primary care setting. The SILVER-AP study. *Aten. Primaria.* 50(6), 359–367 (2018).
28. de la Figuera M, Prieto MA, Marín N, Egocheaga I, Cinza S. Differences in the management of patients with atrial fibrillation according to whether primary care or the specialist initiates treatment with direct oral anticoagulants. The SILVER-AP and BRONCE-AP studies. *Semergen.* 44(5), 323–334 (2018).
- **Shows that in Spain, a significant proportion of patients received lower doses of DOACs than recommended according to the summary of product characteristics.**
29. Connolly SJ, Ezekowitz MD, Yusuf S *et al.* Dabigatran versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* 361(12), 1139–1151 (2009).
30. Patel MR, Mahaffey KW, Garg J *et al.* Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N. Engl. J. Med.* 365(10), 883–891 (2011).
31. Granger CB, Alexander JH, McMurray JJ *et al.* Apixaban versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* 365(11), 981–992 (2011).
32. Giugliano RP, Ruff CT, Braunwald E *et al.*; the ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* 369(22), 2093–2104 (2013).
33. Gundlund A, Staerk L, Fosbøl EL *et al.* Initiation of anticoagulation in atrial fibrillation: which factors are associated with choice of anticoagulant? *J. Intern. Med.* 282(2), 164–174 (2017).
34. Basaran O, Filiz Basaran N, Cekic EG *et al.* PRescriptiOn PAttERns of oral anticoagulants in nonvalvular atrial fibrillation (PROPER study). *Clin. Appl. Thromb. Hemost.* 23(4), 384–391 (2017).
- **Shows that the inappropriate use of oral anticoagulants was common with both DOACs and vitamin K antagonists.**
35. Whitworth MM, Haase KK, Fike DS, Bharadwaj RM, Young RB, MacLaughlin EJ. Utilization and prescribing patterns of direct oral anticoagulants. *Int. J. Gen. Med.* 10, 87–94 (2017).
36. Larock AS, Mullier F, Sennesael AL *et al.* Appropriateness of prescribing dabigatran etexilate and rivaroxaban in patients with nonvalvular atrial fibrillation: a prospective study. *Ann. Pharmacother.* 48(10), 1258–1268 (2014).
37. Chowdhry U, Jacques A, Karovitch A, Giguère P, Nguyen ML. Appropriateness of dabigatran and rivaroxaban prescribing for hospital inpatients. *Can. J. Hosp. Pharm.* 69(3), 194–201 (2016).
38. Nielsen PB, Skjoth F, Sogaard M, Kjaldgaard JN, Lip GY, Larsen TB. Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *BMJ* 356, j510 (2017).
39. Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA. Non-vitamin K antagonist oral anticoagulant dosing in patients with atrial fibrillation and renal dysfunction. *J. Am. Coll. Cardiol.* 69(23), 2779–2790 (2017).
- **Shows that in clinical practice, many atrial fibrillation patients with renal dysfunction did not receive the adequate dosage of DOACs. In apixaban-treated patients with normal or mildly impaired renal function, this translated into a worse effectiveness with no benefit in safety.**

40. Beyer-Westendorf J, Ebertz F, Förster K *et al.* Effectiveness and safety of dabigatran therapy in daily-care patients with atrial fibrillation. Results from the Dresden NOAC Registry. *Thromb. Haemost.* 113(6), 1247–1257 (2015).
41. Hecker J, Marten S, Keller L *et al.* Effectiveness and safety of rivaroxaban therapy in daily-care patients with atrial fibrillation. Results from the Dresden NOAC Registry. *Thromb. Haemost.* 115(5), 939–949 (2016).
42. Helmert S, Marten S, Mizera H *et al.* Effectiveness and safety of apixaban therapy in daily-care patients with atrial fibrillation: results from the Dresden NOAC Registry. *J. Thromb. Thrombolysis* 44(2), 169–178 (2017).
43. Xu WW, Hu SJ, Wu T. Risk analysis of new oral anticoagulants for gastrointestinal bleeding and intracranial hemorrhage in atrial fibrillation patients: a systematic review and network meta-analysis. *J. Zhejiang. Univ. Sci. B.* 18(7), 567–576 (2017).
44. Laine L. Bleeding with direct oral anticoagulants: the gastrointestinal tract and beyond. *Clin. Gastroenterol. Hepatol.* 15(11), 1665–1667 (2017).
45. Hohnloser SH, Basic E, Nabauer M. Comparative risk of major bleeding with new oral anticoagulants (NOACs) and phenprocoumon in patients with atrial fibrillation: a post-marketing surveillance study. *Clin. Res. Cardiol.* 106(8), 618–628 (2017).