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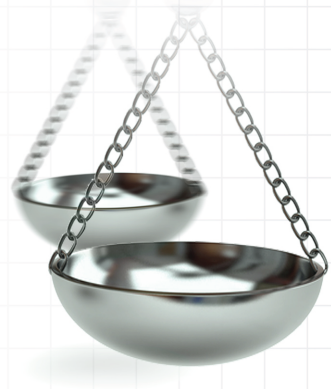

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Type and doses of oral anticoagulants and adherence to anticoagulant treatment in elderly patients with atrial fibrillation: the ESPARTA study

Jose María Mostaza*[,1], Carmen Suárez Fernández[2], Luis Castilla Guerra[3], Josep Maria Suriñach[4], Juan José Tamarit[5], José Luis Diaz Diaz[6], Iluminada García Polo[7], Esther Francia Santamaria[8], María Angeles Fidalgo Fernández[9], Carla de la Guerra Acebal[10], Meliton Francisco Dávila Ramos[11] & Carles Ràfols[12]

[1]Internal Medicine Service, Hospital Carlos III, Madrid 28029, Spain
[2]Internal Medicine Service, Hospital Universitario de La Princesa, Madrid 28006, Spain
[3]Internal Medicine Department, Hospital Virgen Macarena, Sevilla 41009, Spain
[4]Servicio de Medicina Interna, Hospital Vall D Hebron, Barcelona 08035, Spain
[5]Servicio de Medicina Interna, Hospital General de Valencia, Valencia 46014, Spain
[6]Servicio de Medicina Interna, Complejo Universitario Hospitalario de A Coruña, La Coruña 15006, Spain
[7]Internal Medicine Service, Hospital Universitario de La Princesa, Madrid 28006, Spain
[8]Geriatric Unit, Hospital de la Santa Creu iSant Pau, Barcelona 08041, Spain
[9]Internal Medicine Service, Hospital Universitario de Salamanca, Salamanca 37120, Spain
[10]Internal Medicine Service, Hospital de Mendaro, Guipuzcoa 20850, Spain
[11]Internal Medicine Service, Hospital Ntra. Sra. La Candelaria, Santa Cruz de Tenerife, Tenerife 38010, Spain
[12]Departamento Médico, Bayer Hispania SL, Barcelona 08037, Spain
* Author for correspondence: josemaria.mostaza@salud.madrid.org

Aim: To analyze the use of oral anticoagulants in elderly patients with atrial fibrillation in clinical practice. **Patients & methods:** Cross-sectional and multicenter study performed in atrial fibrillation patients ≥75 years treated with oral anticoagulants ≥3 months. **Results:** 837 patients (83.0 ± 5.0 years; CHA_2DS_2-VASc 5.0 ± 1.4; HAS-BLED 2.1 ± 0.9; 70.8% vitamin K antagonists; 29.2% direct oral anticoagulants [DOACs]) were included. Poor adherence was observed in 27.9% of patients. Higher scores in the Pfeiffer's test and FRAIL scale were associated with poorer adherence. Among patients treated with DOACs, 62.3% received the lower doses. Having high $CHADS_2$ score and being older were associated with the use of low doses. **Conclusion:** 28% of patients had a poor adherence to anticoagulant treatment. 62% of patients were treated with the lower doses of DOACs.

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Keywords: adherence • atrial fibrillation • direct oral anticoagulants • dosage • elderly • vitamin K antagonists

The prevalence of atrial fibrillation (AF) markedly rises with age. Thus, more than 10–15% of elderly patients have AF [1]. The management of elderly patients with AF is challenging, since comorbidities, cognitive impairment or polymedication are common in this population [2]. In addition, death and complications associated with AF are increased in elderly patients with AF compared with their younger counterparts [3–5].

Due to the high risk of stroke in elderly patients, all patients aged 75 years or older should receive oral anticoagulation unless contraindicated [6,7]. Paradoxically, rates of anticoagulation decrease as age increases, and this has been associated with a worse prognosis [5]. Some reasons that could explain the underuse of anticoagulation in this population include the higher risk of bleeding in elderly patients, as well as the limitations of vitamin K antagonists (VKA), such as interactions with food or other drugs, periodic monitoring of anticoagulation or frequent dose adjustments [5,8]. Direct oral anticoagulants (DOACs) overcome the great majority of the limitations of VKA and seem safer. Compared with warfarin, the risk of intracranial hemorrhage is decreased by DOACs, regardless of age [9].

Future Medicine

Although the information provided by clinical trials is critical for drug approval, and is often limited to specific subgroups of patients due to strict inclusion or exclusion criteria. In this context, observational studies are important to extend the information from clinical trials to 'real-life' patients. This is particularly relevant in elderly patients that are frequently underrepresented in clinical trials [10].

Due to a number of conditions such as the high number of comorbidities, cognitive impairment or polymedication, adherence to anticoagulant treatment may be hampered in elderly patients with AF. However, there is little information about adherence to anticoagulation in this population and whether the introduction of DOACs in clinical practice may modify medication compliance [11]. On the other hand, although dosage adjustment with DOACs according to different clinical characteristics has been clearly established, it is uncertain whether these recommendations are being followed in elderly patients in clinical practice [12].

The ESPARTA was an observational, cross-sectional and multicenter study aimed to evaluate, in clinical practice, the adherence to the recommendations performed by the Therapeutic Positioning Report of the Spanish Medicine and Sanitary Products Agency [13] about the treatment with oral anticoagulants in patients aged ≥75 years old with nonvalvular AF (NVAF) attended in Internal Medicine Departments in Spain [14]. The list of Investigators involved in the ESPARTA study is available in Supplementary Table 1. In this manuscript, the clinical profile of patients according to the type of oral anticoagulant, the adherence to treatment and the dosage of DOACs, as well as the variables associated with the use of DOACs (vs VKA), good adherence to treatment (vs poor adherence) and the dosage of DOACs (low doses vs regular doses) were analyzed.

Methods

In the ESPARTA study, patients aged ≥75 years old, with a diagnosis of NVAF attended in Internal Medicine units (hospitalization or outpatients) in Spain, treated with oral anticoagulants within the 3 months previous the inclusion, that had started treatment with oral anticoagulants before the inclusion period and that had provided signed informed consent were consecutively included. Patients were excluded if they had mitral stenosis or other significant valvulopathy that required performed or planned specific treatment (i.e., prosthetic valve, valvuloplasty), participated in clinical trials involving the use of DOACs in the 6 months before inclusion, or if they were unable to understand or fulfill the questionnaires of the study. The study was approved by the Clinical Research Ethics Committee of Hospital Universitario de la Princesa de Madrid and endorsed by the local ethic committees of the participating centers [14].

The study was performed in 63 Internal Medicine units throughout Spain, according to clinical practice. The participating sites were representative sample of all such sites in Spain. The inclusion period started on October 2015 and ended on March 2016. The study involved a single visit that coincided with one of the patient's regular follow-up visits. The biodemographic and clinical data were collected from the medical history during the physician interview and recorded by each investigator in an electronic case report form [14].

The thromboembolic risk was determined by the $CHADS_2$ and CHA_2DS_2-VASc scales and the risk of bleeding by the HAS-BLED scale [15,16]. The type of oral anticoagulant (VKA vs DOACs) was recorded, as well as the dosage of DOACs: rivaroxaban 20 mg once daily, dabigatran 150 mg twice daily and apixaban 5 mg twice daily were considered as the regular doses of DOACs and rivaroxaban 15 mg once daily, dabigatran 110 mg twice daily and apixaban 2.5 mg twice daily as the low doses of DOACs [12]. The adequacy of anticoagulant treatment was analyzed according to the recommendations performed by the Spanish Medicine and Sanitary Products Agency about the use of oral anticoagulants in NVAF patients (Supplementary Table 2) [13]. In this report, recommendations about the indications/contraindications of anticoagulation, when to use VKA or DOACs or the dosage of DOACs were given [13].

Polymedication was defined as the regular intake of at least five tablets daily at the moment of the visit. Comorbidity was determined according to the Charlson Comorbidity Index. High comorbidity was defined as having a Charlson Comorbidity Index of 3 or more [17]. Cognitive function was assessed using the Pfeiffer's test, defining the presence of cognitive impairment as having a score of 3 or more [18]. Fragility was determined with the FRAIL scale. The fragile patient was defined as having a score of 3 or more in the FRAIL scale [19]. Physicians asked the patient or their relatives whether patient had partial dependency (need help for at least one of the following activities: personal care, eating, getting dressed or moving), total dependency (need help for all previous activities) or no dependency. Adherence to treatment with oral anticoagulants was determined by using the Morisky–Green test. Good adherence was defined as an average adherence to oral anticoagulation of more than 80% [20].

Table 1. Clinical characteristics of the study population according to the oral anticoagulant used.

Variable	Total (n = 837, 100%)	VKA (n = 593, 70.8%)	DOAC (n = 244, 29.2%)	p-value
Biodemographic data				
Age (years)	83.0 ± 5.0	83.2 ± 5.1	82.6 ± 4.8	NS
Gender male (%)	48.7	47.0	52.9	NS
Place where patients live (%):				
– Home	93.8	93.3	95.1	NS
– Residence	6.2	6.7	4.9	–
Dependency (%):				
– No dependency	55.6	55.0	57.0	NS
– Partial dependency	37.8	38.8	35.2	–
– Total dependency	6.7	6.2	7.8	–
Type of AF (%):				
– Paroxysmal	13.2	11.3	18.0	–
– Persistent	3.5	2.2	6.6	–
– Permanent	83.3	86.5	75.4	0.0001
Body weight (kg)	73.7 ± 13.9	73.4 ± 13.6	74.4 ± 14.7	NS
Cardiovascular risk factors				
Hypertension (%)	84.3	86.2	79.9	0.02
Diabetes mellitus (%)	39.1	38.8	39.8	NS
Cardiovascular disease				
Heart failure (%)	62.7	64.4	58.6	NS
Cerebrovascular disease (%)	19.2	19.2	19.3	NS
Coronary artery disease (%)	21.6	22.6	19.3	NS
Peripheral artery disease (%)	8.1	8.3	7.8	NS
Renal insufficiency (%)	7.9	7.6	8.6	NS
Creatinine clearance (ml/min):	50.7 ± 21.9	49.7 ± 21.3	53.3 ± 23.2	NS
– >80 ml/min (%)	9.4	9.1	10.1	–
– 50–80 ml/min (%)	36.7	35.9	38.5	NS
– 30–49 ml/min (%)	38.5	38.1	39.4	–
– 15–29 ml/min (%)	14.7	15.9	12.0	–
– <15 ml/min (%)	0.7	1.0	0	–
Thromboembolic and bleeding risk				
Mean $CHADS_2$ score:	3.2 ± 1.2	3.3 ± 1.2	3.2 ± 1.2	NS
– High thromboembolic risk (%)	94.7	95.3	93.4	NS
Mean CHA_2DS_2-VASc score:	5.0 ± 1.4	5.1 ± 1.4	4.9 ± 1.4	NS
– High thromboembolic risk (%)	100	100	100	NS
Mean HAS-BLED score:	2.1 ± 0.9	2.2 ± 0.9	1.8 ± 0.8	<0.0001
– High bleeding risk (%)	28.9	32.7	20.5	0.0005
– Prior bleeding (%)	17.6	14.3	25.4	0.00001
Other conditions				
Charlson Comorbidity Index:	2.7 ± 1.9	2.7 ± 1.9	2.8 ± 2.1	NS
– Mean score adjusted for age	6.6 ± 2.0	6.6 ± 2.0	6.5 ± 2.2	NS
– High comorbidity (%)	48.1	47.4	50.0	NS
Pfeiffer's test	1.9 ± 2.1	2.0 ± 2.1	1.8 ± 2.3	0.01
Cognitive impairment (%)	32.3	34.2	27.5	0.05
FRAIL scale	2.1 ± 1.4	2.1 ± 1.4	2.1 ± 1.4	NS
Falls (%)	25.1	25.0	25.4	NS
Polymedication (%)	91.5	92.6	88.9	NS

AF: Atrial fibrillation; DOAC: Direct oral anticoagulant; NS: Not significant; VKA: Vitamin K antagonist.

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. In the bivariate analysis to compare two means, the nonparametric Mann–Whitney U test was performed. To compare percentages, the χ^2 test or Fisher test was used, according to the sample size.

Stepwise binary logistic regression analyses were performed to identify those variables associated with the use of DOACs (vs VKA), the adherence to treatment (good adherence vs poor adherence) and the use of low doses of

Table 2. Variables associated with the use of direct oral anticoagulant (vs vitamin K antagonist)[†].

Variables	OR (95% CI)	p-value
Prior bleeding	5.521 (3.291–9.263)	<0.0001
$CHADS_2$ score (high vs low)	1.292 (1.102–1.515)	0.0016
Hypertension	0.548 (0.319–0.940)	0.0290
Type of AF:		
– Paroxysmal	–	0.0041
– Persistent	1.320 (0.498–3.502)	–
– Permanent	0.499 (0.300–0.829)	–
Hemorrhagic risk (HAS-BED score):		
– Intermediate	–	0.0281
– High	0.437 (0.208–0.915)	–
HAS-BLED score (high vs low)	0.256 (0.171–0.383)	<0.0001

[†]The variables not achieving statistical significance and excluded from the model were: age, gender, place where patients live, dependency, body weight, diabetes, heart failure, cerebrovascular disease, coronary artery disease, peripheral artery disease, renal insufficiency, Charlson Comorbidity Index, FRAIL scale, falls and polymedication.
AF: Atrial fibrillation; OR: Odds ratio.

DOACs (vs regular doses). Those variables with a p-value < 0.10 in the univariate analysis were included in the multivariate analysis. Odds ratios and their respective 95% CIs were used to describe the results of the multivariate analyses. Statistical significance was set at a p-value < 0.05. The statistical analysis was performed using the SAS statistics package, version 9.4 (SAS, NC, USA).

Results

The study included 854 patients, 17 (2%) of whom were excluded from the final analysis due to improperly recorded or missing data in the electronic case report form. Finally, 837 patients were included for assessment (mean age 83.0 ± 5.0 years old; 48.7% men; mean $CHADS_2$ score 3.2 ± 1.2; mean CHA_2DS_2-VASc score 5.0 ± 1.4; mean HAS-BLED score 2.1 ± 0.9; mean Charlson Comorbidity Index 2.7 ± 1.9). According to Charlson Comorbidity Index, Pfeiffer's test and FRAIL scale, comorbidity was high in 48.1% of patients, 32.3% of patients had some degree of cognitive impairment and 43.3% of patients were fragile, respectively. 17.4% of patients lived alone. Overall, 70.8% of patients were taking VKA (mean time on treatment 73.3 ± 59.3 months) and 29.2% DOACs (mean time on treatment 16.6 ± 14.3 months). The clinical characteristics of patients were analyzed according to the type of oral anticoagulant (Table 1). Permanent AF, hypertension and the risk of bleeding were more common in patients taking VKA compared with those patients taking DOACs. There was a trend to have more cognitive impairment in the group of patients taking VKA. In the multivariate analysis, hypertension, permanent AF, high hemorrhagic risk and a higher HAS-BLED score were associated with the use of VKA, whereas prior bleeding and a higher $CHADS_2$ score were associated with the prescription of DOACs (Table 2).

According to Morisky–Green test, 27.9% of patients had a poor adherence to anticoagulant treatment (27.0% in those patients taking VKA and 29.9% in those patients taking DOACs). Patients with a good adherence to treatment had a higher thromboembolic risk. By contrast, cognitive impairment and fragility were more common in patients with a poor adherence to treatment (Table 3). In the multivariate analysis, having a high $CHADS_2$ score was associated with a good adherence to treatment, whereas higher scores in the Pfeiffer's test and FRAIL scale were related with poor adherence to treatment (Table 4).

Overall, 244 patients were taking DOACs. According to the recommendations performed by the Spanish Medicine and Sanitary Products Agency, about the use of oral anticoagulants in NVAF patients, 57.0% of patients were taking DOACs adequately (65.5% of patients treated with rivaroxaban; 56.3% with dabigatran and 46.5% with apixaban; p = 0.029). Among patients taking DOACS, 37.7% were taking the regular doses and 62.3% the lower doses. Compared with the regular doses, the low doses of DOACs were more commonly prescribed in women and polymedicated patients as well as in patients with heart failure, prior cerebrovascular disease and renal insufficiency. In addition, patients taking the low doses of DOACs were older, partial or total dependent, and had a higher thromboembolic and bleeding risk. The scores of the Charlson Comorbidity Index, Pfeiffer's test and FRAIL scale were higher in the group of patients taking the low doses of DOACs. By contrast, body weight was higher in patients taking the regular doses of DOACs. There was a trend to have more permanent AF in patients taking the low doses of DOACs (Table 5). In the multivariate analysis, having a high $CHADS_2$ score and being

Table 3. Clinical profile of patients according to the adherence to treatment.

Variable	Good adherence (n = 603, 72.1%)	Poor adherence (n = 233, 27.9%)	p-value
Biodemographic data			
Age (years)	83.1 ± 5.0	82.7 ± 5.0	NS
Gender male (%)	48.9	48.5	NS
Place where patients live (%): – Home – Residence	 94.0 6.0	 93.1 6.9	 NS –
Dependency (%): – No dependency – Partial dependency – Total dependency	 55.4 37.1 7.5	 56.2 39.1 4.7	 – NS –
Type of AF (%): – Paroxysmal – Persistent – Permanent	 13.8 3.0 83.3	 12.0 4.7 83.3	 NS – –
Body weight (kg)	73.8 ± 13.7	73.4 ± 14.4	NS
Cardiovascular risk factors			
Arterial hypertension (%)	85.1	82.4	NS
Diabetes mellitus (%)	40.8	34.8	NS
Cardiovascular disease			
Heart failure (%)	64.3	72.9	NS
Cerebrovascular disease (%)	19.9	17.6	NS
Coronary artery disease (%)	22.1	20.6	NS
Peripheral artery disease (%)	7.8	9.0	NS
Renal insufficiency (%)	7.3	9.4	NS
Creatinine clearance (ml/min): – >80 ml/min (%) – 50–80 ml/min (%) – 30–49 ml/min (%) – 15–29 ml/min (%) – <15 ml/min (%)	50.6 ± 21.6 8.5 37.9 38.7 14.4 0.6	51.1 ± 22.8 12.0 33.3 38.0 15.6 1.0	NS – NS – – –
Thromboembolic and bleeding risk			
Mean $CHADS_2$ score: – High thromboembolic risk (%)	3.3 ± 1.2 95.0	3.1 ± 1.2 94.0	0.04 NS
Mean CHA_2DS_2-VASc score: – High thromboembolic risk (%)	5.1 ± 1.4 100	4.9 ± 1.4 100	NS NS
Mean HAS-BLED score: – High bleeding risk (%) – Prior bleeding (%)	2.0 ± 0.9 27.6 17.9	2.1 ± 0.9 31.8 16.3	NS NS NS
Other conditions			
Charlson Comorbidity Index: – Mean score adjusted for age – High comorbidity (%)	2.7 ± 1.9 6.6 ± 2.0 49.1	2.7 ± 2.1 6.5 ± 2.2 45.9	NS NS NS
Pfeiffer's test	1.8 ± 2.1	2.2 ± 2.1	0.004
Cognitive impairment (%)	29.0	40.8	0.001
FRAIL scale	2.0 ± 1.4	2.3 ± 1.5	0.003
Falls (%)	25.4	24.0	NS
Polymedication (%)	91.7	91.4	NS

AF: Atrial fibrillation; NS: Not significant.

older were independently associated with the use of the low doses of DOACs, whereas a higher body weight and greater glomerular filtration rates were associated with the use of regular doses of DOACs (Table 6).

Discussion

In our study, a wide sample of anticoagulated elderly patients with AF was analyzed. Despite these patients had a high thromboembolic risk ($CHADS_2$ score = 3.2; CHA_2DS_2-VASc score = 5.0), less than 30% of patients had a high bleeding risk. This is in the line with current recommendations about the need for anticoagulating the

Table 4. Variables associated with good adherence to treatment.

Variables	OR (95% CI)	p-value
$CHADS_2$ score (high vs low)	1.234 (1.071–1.422)	0.0036
Pfeiffer's test (high vs low)	0.920 (0.854–0.992)	0.0297
FRAIL scale (high vs low)	0.828 (0.734–0.935)	0.0023

The variables not achieving statistical significance and excluded from the model were: age, gender, place where patients live, dependency, type of AF, body weight, arterial hypertension, diabetes, heart failure, cerebrovascular disease, coronary artery disease, peripheral artery disease, renal insufficiency, CHA_2DS_2-VASc score, HAS-BLED score, Charlson Comorbidity Index, falls and polymedication.
AF: Atrial fibrillation; OR: Odds ratio.

majority of elderly patients with AF [6,21]. On the other hand, although one of the concerns about anticoagulation is the risk of falls, it has been determined that though caution should be taken, the indication of anticoagulation should be independent of the risk of falls [7]. In our study, falls were independent of the type of oral anticoagulant, the adherence to treatment or the dosage of DOACs.

It has recently been reported that among elderly patients with NVAF, compared with warfarin, treatment with DOACs is associated with a lesser risk of stroke and intracranial bleeding [22]. Surprisingly, in our study, VKAs were more commonly prescribed in patients with a high hemorrhagic risk. By contrast, prior bleeding and a high thromboembolic risk were associated with the use of DOACs. This means that in elderly patients with a high risk of bleeding, DOACs are mainly used only when a hemorrhagic episode occurs.

It was quite unexpected that there was a trend to have more cognitive impairment among patients taking VKA compared with DOACs. This issue should be evaluated in-depth in future studies.

Since anticoagulation reduces the risk of stroke in AF patients, assuring a good adherence to oral anticoagulation is mandatory [21,23,24]. In our study, nearly 30% of patients had a poor adherence to treatment. A high thromboembolic risk was associated with good adherence to treatment, whereas cognitive impairment and fragility were related with poor adherence. However, in contrast to previous information [11], polymedication was not associated with medication adherence in our study. It has been reported that complexity of treatment (number of tablets and frequency of administration) and some patients' clinical characteristics, such as fragility, cognitive impairment, co-morbidities or polymedication, have a relevant impact on medication adherence [11]. However, it should be noted that many adherence researchers remain skeptical of self-reported measures of adherence, especially for accurately identifying patients who are not adherent [25]. As a result, it is likely that the finding that the study population had 30% bad adherence may be a conservative estimate because it is possible that some nonadherent patients were misclassified as adherent patients. Consequently, simplification of treatment through a reduction in the number of tablets, or using drugs with a lesser risk of interactions is mandatory to improve medication adherence. In addition, to improve medication adherence in elderly patients with NVAF may be important to assure a good family and/or community support, particularly in fragile patients or in those patients with cognitive impairment [11].

Another important point that was analyzed was the use of DOACs. In our study, a total of 244 elderly patients with NVAF were taken DOACs. Importantly, 43% of patients did not follow adequately at least one the recommendations performed by the Spanish Medicine and Sanitary Products Agency [13,14]. In addition, the majority of patients (62.3%) received the low doses of DOACs. In the last years, a number of small studies have also analyzed the dosage of DOACs used in clinical practice. Thus, in a study that included 148 patients with AF treated with warfarin (n = 73), rivaroxaban (n = 39) and dabigatran (n = 36), dosage was not appropriate in 77, 23 and 42% of patients, respectively [26]. In other study that included 69 patients, inappropriate use of DOACs was common and more than a quarter of patients were taking a wrong dose of DOACs. Importantly, this led to higher rates of adverse events, including stroke [27]. Although DOACs are administered at fixed doses, dosage of DOACs should be adjusted according to different clinical characteristics. However, these characteristics vary among different DOACs: dosage of rivaroxaban should be adjusted according to renal function; apixaban according to renal function, body weight and age; dabigatran according to renal function, age, risk of bleeding and the use of verapamil; and edoxaban according to renal function, body weight and the use of potent P-gp inhibitors [12]. In our study, the proper use of DOACs was more common with rivaroxaban, likely due to a lesser complexity in the dosage adjustment.

On the other hand, our data showed that a high thromboembolic risk (assessed by $CHADS_2$ and the CHA_2DS_2-VASc scores) and being older were independently associated with the use of the low doses of DOACs, whereas a higher body weight and greater filtration glomerular rates were associated with the use of regular doses of DOACs.

Table 5. Clinical profile of patients according to the dose of direct oral anticoagulants.

Variable	Low dose (n = 152, 62.3%)	Regular dose (n = 92, 37.7%)	p-value
Biodemographic data			
Age (years)	83.8 ± 4.8	80.5 ± 4.2	<0.0001
Gender male (%)	48.0	60.9	0.05
Place where patients live (%): – Home – Residence	 94.7 5.3	 95.7 4.3	 NS –
Dependency (%): – No dependency – Partial dependency – Total dependency	 50.0 41.4 8.6	 68.5 25.0 6.5	 0.01 – –
Type of AF (%): – Paroxysmal – Persistent – Permanent	 14.5 5.3 80.3	 23.9 8.7 67.4	 – – NS
Body weight (kg)	71.6 ± 14.7	78.9 ± 13.7	0.0002
Cardiovascular risk factors			
Arterial hypertension (%)	82.2	76.1	NS
Diabetes mellitus (%)	43.4	33.7	NS
Cardiovascular disease			
Heart failure (%)	65.8	46.7	0.003
Cerebrovascular disease (%)	23.7	11.9	0.02
Coronary artery disease (%)	21.1	16.3	NS
Peripheral artery disease (%)	5.9	10.8	NS
Renal insufficiency (%)	12.5	2.2	0.005
Creatinine clearance (ml/min): – >80 ml/min (%) – 50–80 ml/min (%) – 30–49 ml/min (%) – 15–29 ml/min (%) – <15 ml/min (%)	46.6 ± 20.4 5.3 29.3 48.1 17.3 0	65.1 ± 23.3 18.7 54.7 24.0 2.7 0	<0.0001 – <0.0001 – – –
Thromboembolic and bleeding risk			
Mean $CHADS_2$ score: – High thromboembolic risk (%)	3.4 ± 1.2 96.1	2.8 ± 1.1 89.1	0.0005 0.03
Mean CHA_2DS_2-VASc score: – High thromboembolic risk (%)	5.1 ± 1.4 100	4.5 ± 1.4 100	0.0002 NS
Mean HAS-BLED score: – High bleeding risk (%) – Prior bleeding (%)	1.8 ± 0.9 25.7 25.0	1.6 ± 0.7 12.0 26.1	NS 0.01 NS
Other conditions			
Charlson Comorbidity Index: – Mean score adjusted for age – High comorbidity (%)	3.0 ± 2.1 6.9 ± 2.2 55.9	2.4 ± 2.0 6.0 ± 2.0 40.2	0.02 0.0009 0.04
Pfeiffer's test	2.0 ± 2.4	1.3 ± 1.9	0.008
Cognitive impairment (%)	30.3	22.8	NS
FRAIL scale	2.3 ± 1.3	1.7 ± 1.5	0.001
Falls (%)	24.3	27.2	NS
Polymedication (%)	92.8	82.6	0.01

AF: Atrial fibrillation; NS: Not significant.

All these data suggest that dose adjustment of DOACs is not properly performed in some patients. It is likely that some physicians may confuse dose adjustment among different DOACs. This is important, since using lower doses of DOACs than recommended could reduce the efficacy of DOACs for the prevention of stroke or systemic embolism in patients with NVAF [12]. Although medical education programs are needed to improve the correct use of DOACs, using those DOACs easier to adjust might reduce the errors performed in this context.

The most important limitation of this study derives from its observational and cross-sectional design that does not allow controlling some potential confounders. However, this is the design that better represents clinical practice. In

Table 6. Variables associated with the use of low doses of direct oral anticoagulants (vs regular doses) in the overall study population.

Variables	OR (95% CI)	p-value
$CHADS_2$ score (high vs low)	1.392 (1.054–1.839)	0.0197
Age (old vs young)	1.143 (1.058–1.236)	0.0008
Body weight (high vs low)	0.973 (0.952–0.996)	0.0202
Glomerular filtration (high vs low)	0.968 (0.951–0.985)	0.0003

The variables not achieving statistical significance and excluded from the model were: place where patients live, type of AF, arterial hypertension, diabetes, coronary artery disease, peripheral artery disease, HAS-BLED score, cognitive impairment and falls.
AF: Atrial fibrillation; OR: Odds ratio.

addition, patients were consecutively included and data were meticulously recorded what may significantly reduce the impact of this potential bias.

Conclusion

In conclusion, among elderly patients with NVAF treated with oral anticoagulants in the Internal Medicine Departments in Spain, VKA were more commonly prescribed in patients with a high hemorrhagic risk and DOACs in patients with prior bleeding or a high thromboembolic risk. Nearly 30% of patients had a poor adherence to anticoagulant treatment. Finally, among patients treated with DOACs, more than 60% were treated with the low doses. A high thromboembolic risk and being older were independently associated with the use of low doses of DOACs, whereas a higher body weight and greater filtration glomerular rates with regular doses. These data strongly suggest that physicians confuse dose adjustment among different DOACs. This occurred to a lesser extent with rivaroxaban.

Summary points

- Observational studies are important to extend the information from clinical trials to 'real-life' patients. This is particularly relevant in elderly patients that are frequently underrepresented in clinical trials.
- In this study, the clinical profile of elderly patients with nonvalvular atrial fibrillation (NVAF) according to the type of oral anticoagulant, the adherence to treatment and the dosage of direct oral anticoagulants (DOACs), as well as the variables associated with the use of DOACs (vs vitamin K antagonist [VKA]), good adherence to treatment (vs poor adherence) and the dosage of DOACs (low doses vs regular doses) were analyzed.

Methods

- Observational, cross-sectional and multicenter study performed in patients ≥75 years with NVAF and stable treatment with oral anticoagulants at least 3 months before inclusion.

Results

- A total of 837 patients (83.0 ± 5.0 years, CHA_2DS_2-VASc 5.0 ± 1.4, HAS-BLED 2.1 ± 0.9, Charlson Comorbidity Index 2.7 ± 1.9) were included.
- 70.8% of patients were taking VKAs and 29.2% DOACs.
- Hypertension, permanent AF and a higher HAS-BLED score were associated with the use of VKA, whereas prior bleeding and a higher $CHADS_2$ score with DOACs.
- Poor adherence to treatment was observed in 27.9% of patients. Having a high $CHADS_2$ score was associated with good adherence, whereas higher scores in the Pfeiffer's test and FRAIL scale with a poorer adherence.
- Among patients treated with DOACs, 62.3% received the lower doses of DOACs. Having a high $CHADS_2$ score and being older were associated with the use of low doses of DOACs, and a higher body weight and greater glomerular filtration rates with the regular doses of DOACs.

Discussion

- Among elderly patients with NVAF, compared with warfarin, treatment with DOACs is associated with a lesser risk of stroke and intracranial bleeding. Despite that, in our study, VKAs were more commonly prescribed in patients with a high hemorrhagic risk.
- Nearly 30% of patients had a poor adherence to treatment. To improve medication adherence in elderly patients with NVAF is important to reduce outcomes.
- The majority of patients (62.3%) treated with DOACs received the low doses. In the last years, a number of small studies have reported similar results.

Conclusion

- Among elderly anticoagulated patients, VKAs were more commonly prescribed in patients with a high hemorrhagic risk and DOACs in patients with prior bleeding or a high thromboembolic risk.
- More than 60% of patients with DOACs were treated with the lower doses.
- Nearly 30% had a poor adherence to anticoagulant treatment.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2017-0034

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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.

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