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Patients with non-valvular atrial fibrillation on Vitamin K antagonists or direct-acting oral anticoagulants: patients profile and long-term follow-up outcomes

Pacientes con fibrilación auricular no valvular tratados con antivitamina K o anticoagulantes directos: perfil de paciente y efectos a largo plazo

Andrea Sigismondi[1], Santiago J. Camacho-Freire[1], Javier León-Jiménez[1], Guillermo Isasti-Aizpurva[1], María D. García-Lizana[1], José I. Morgado-García de Polavieja[1], Francisco J. Caro-Fernández[1], Jessica Roa-Garrido[1], Francisco Navarro-Roldán[2], and José F. Díaz-Fernández[1]*

[1]Department of Cardiology, Hospital Universitario Juan Ramón Jiménez; [2]Department of Integrated Sciences, Faculty of Experimental Sciences, Universidad de Huelva. Huelva, Spain

Abstract

Introduction: *The arrival of direct-acting oral anticoagulants (DOACs) has led to a change in the management of non-valvular atrial fibrillation (NVAF) in recent years. The objectives of this study are to determine the level of therapeutic control of anticoagulation with Vitamin K antagonists (VKA) and its possible involvement in major adverse cardiovascular events (MACE) and to evaluate the differences between the group on VKA with respect to the group on DOACs.* **Patients and methods:** *Prospective cohort study that included consecutive patients diagnosed with NVAF in cardiology consultations with a clinical follow-up of 18 months. Demographic, clinical, and analytical differences between groups were analyzed, including the level of therapeutic control of anticoagulation on the VKA group and its association with MACE.* **Results:** *Overall, 273 patients were included: 46.5% on VKA, 42.5% on DOACs, and 11% without antithrombotic treatment. Patients on VKA spent 62.1% of their time within the therapeutic range (TTR by the Rosendaal formule). There were no differences in MACE depending on anticoagulation control. The DOACs group presented lesser MACE rate than the VKA group (13.4 vs. 4.3%; 0.90; hazard ratio [HR] 0.90; 0.83-0.98 p = 0.01) with lower cardiovascular mortality (0.0 vs. 5.5%; HR, 0.94; 0.90-0.98; p = 0.01) and total mortality (0.9 vs. 12.6%; HR, 0.88; 0.82-0.94; p < 0.01) although without significant differences in hemorrhagic (0.9 vs. 4.7 %; p = 0.07), or ischemic events (2.6 vs. 0.8%, p = 0.27).* **Conclusions:** *Patients on VKA have a different clinical profile than those who receive DOACs. Patients on VKA have inadequate control of the anticoagulation in quite half of the cases. The VKA group presented more MACE than the DOACs group.*

Key words: *Non-valvular atrial fibrillation. Vitamin K antagonists. Direct-acting oral anticoagulant. Anticoagulation. REACOH study.*

Correspondence:
*Andrea Sigismondi
E-mail: sigismondiandrea@gmail.com

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Resumen

Introducción: *La llegada de los anticoagulantes directos (ACD) ha supuesto un cambio en el tratamiento de la fibrilación auricular no valvular (FANV) en los últimos años. Los objetivos de este estudio son determinar el grado de control de la anticoagulación con antivitamina K (AVK) y su posible implicación en efectos cardiovasculares adversos mayores (ECAM) y evaluar las diferencias entre el grupo en tratamiento con AVK respecto del grupo con ACD.* **Pacientes y métodos:** *Estudio de cohorte prospectivo que incluyó a pacientes consecutivos diagnosticados con FANV valorados en el Servicio de Cardiología con un seguimiento de 18 meses. Se analizaron diferencias demográficas, clínicas y analíticas entre grupos, incluido el grado de control de la anticoagulación del grupo AVK y su posible relación con ECAM.* **Resultados:** *Se incluyó a 273 pacientes: 46.5% tratados con AVK, 42.5% con ACD y 11% sin tratamiento anticoagulante. El control de la anticoagulación con AVK fue del 62.1%, sin diferencias en ECAM en función de control. El grupo ACD presentó menos ECAM que el grupo de AVK (13.4 vs. 4.3%; HR, 0.90; 0.83-0.98; p = 0.01), con una menor mortalidad cardiovascular (0.0 vs. 5.5%; HR, 0.94; 0.90-0.98; p = 0.01) y total (0.9 vs. 12.6%; HR, 0.88; 0.82-0.94; p < 0,01), aunque sin diferencias significativas en eventos hemorrágicos (0.9 vs. 4.7%; p = 0.07) ni isquémicos (2.6 vs. 0.8%; p = 0.27).* **Discusión:** *Los pacientes con AVK poseen un perfil clínico diferente en comparación con los que reciben ACD. El control de anticoagulación del grupo de AVK fue inadecuado en casi la mitad de los casos. El grupo de AVK presentó más ECAM que el grupo de ACD.*

Palabras clave: *Fibrilación auricular no valvular. Antagonistas de la vitamina K. Anticoagulantes directos. Anticoagulación. Estudio REACOH.*

Introduction

Atrial fibrillation (AF) represents one of the main causes of cardiovascular morbidity and mortality, and its prevalence increases with age. Regularly, non-valvular AF (NVAF) has been defined as AF in the absence of rheumatic valve disease (at least moderate mitral stenosis) and cardiac mechanical valve prosthesis[1].

Vitamin K antagonist (VKA) drugs have been systematically used for the prevention of thromboembolic episodes in patients with AF for decades. Although VKAs have proven effective in ischemic stroke reduction in multiple randomized clinical trials, there are several reasons that have driven to their underutilization: narrow therapeutic spectrum, interactions with drugs and foods, and the requirement of International Normalized Ratio (INR) strict periodic surveillance[2-6]. In turn, poor anticoagulation control with VKA has been documented in national studies, as well as a possible relationship with certain factors, such as kidney disease, use of nonsteroidal anti-inflammatory or antiplatelet drugs, lack of treatment with angiotensin-receptor blockers, belonging to the female gender, diabetes mellitus, dietary habits, and polypharmacy. In these national studies, a poor degree of anticoagulation control has been identified, which ranges from 39.4 to 47.3% of patients, as determined by the time within the therapeutic range (TTR) calculated using the Rosendaal formula[7-10].

In recent years, the development of new direct anticoagulant (DAC) drugs that inhibit thrombin or Factor Xa has been observed[11-14]. These molecules offer a potential advantage over to VKA, since they have a more predictable pharmacological profile, a fixed daily administration and less pharmacological and alimentary interactions. In their different pivotal clinical trials, and later in large real-life records, they have shown at least equal safety and efficacy versus VKA for stroke and systemic thromboembolism prevention, with data that have been confirmed in recent meta-analyses[15]. However, these results seem to differ according to geographical areas and study populations[16].

In the light of new evidence, European and American[1] clinical practice guidelines for the treatment of AF propose the use of a DAC as the first option in patients with NVAF. However, implementation in clinical practice by professionals in “real-life” is lower than expected[12].

The purpose of this study was to know the anticoagulation oral treatment of patients with NVAF in this area and analyze, on the one hand, the control of the degrees of anticoagulation in patients on treatment with VKA and possible factors related to poor control and, on the other hand, the major adverse cardiovascular effects (MACE) occurred in the DAC group in comparison with the VKA (acenocoumarol) group in the authors’ hospital area.

Patients and methods

A prospective, cohort, and observational study was designed, where patients with NVAF attended to in outpatient services of the hospital cardiology department for 3 consecutive months (May 2015-July 2015) were included in the study. The inclusion criteria were the time window and a NVAF diagnosis, regardless of age and gender. Patients diagnosed with valvular AF, i.e., patients with mechanical valve prosthesis or individuals with at least moderate mitral stenosis and those who did not grant their consent for data collection were excluded from the study. Patients who attend the outpatient clinic of the cardiology department are referred by the primary care physician, other specialists, or are on follow-up after hospitalization in the cardiology department. The corresponding ethical committee of the hospital center approved the study protocol in 2015.

The assignment of one or another drug to the patients has been a free decision of the different doctors who have instituted the treatment. The factors that have guided this choice have been the personal experience of each professional, patient clinical characteristics, and the recommendations of current clinical practice guidelines. This way, describing the characteristics of anticoagulation in clinical practice has been attempted, without external influences determining treatment allocation, and without any interference of manufacturers.

Demographic, clinical, and analytical data were collected, and an 18-month prospective clinical follow-up was carried out.

Clinical and analytical and differences, as well the occurrence of MACE between the VKA and DAC groups were analyzed during follow-up, which included cardiovascular and all-cause death, hemorrhagic episodes (hemorrhagic stroke, intracranial bleeding, and gastrointestinal major bleeding), and ischemic events (ischemic stroke, peripheral embolism, and myocardial infarction). For thrombotic and hemorrhagic risk evaluation, the recommended scales, CHA_2DS_2-VASc, $CHADS_2$ and HASBLED, were used[1,17,18].

In the authors' hospital area, acenocoumarol was used as VKA in all cases. To calculate the degree of anticoagulation control with VKA, TTR was used by the direct method and by the Rosendaal formula[19]. Poor control was considered when TTR did not reach 65% (Group A) and good control (Group B) when it exceeded 65%. Differences between both groups were analyzed.

Discrete variables are presented as the number and percentage and were compared with the Chi-square test or Fisher's exact test (if expected values in the cells were < 5). Continuous variables are presented as the mean ± standard deviation and were compared using the Student's t-test. Continuous variables that did not have a normal distribution are presented as medians and interquartile ranges. In the case of asymmetric distributions, a non-parametric test (Mann–Whitney U-test) was used. The multivariate analysis was based on logistic regression and Cox proportional hazards test to identify mortality factors during follow-up. Multivariate models were applied using selected variables that were statistically related in the univariate analysis. The receiver operating characteristics curve was used to determine the predictive value of the model obtained in the logistic regression multivariate analysis. To assess the differences between the VKA and DAC groups, as well as between the groups with well and poorly controlled INR, a proportional risk model with Cox regression was used for the analysis of adverse effects during the follow-up (presented as hazard ratios [HR] with their confidence intervals).

Finally, the probability of survival and events during follow-up has been calculated using the Kaplan–Meier test, while Mantel log-rank test was used to compare survival curves between subgroups. The statistical analysis was carried out with the SPSS 22 software. $p < 0.05$ was considered statistically significant.

Results

Clinical profile and treatment of patients with NVAF

Up to 127 of patients (46.5%) received VKA (Group 1), 116 (42.5%) received one DAC (Group 2), and 30 (11%) received no treatment (Group 3). In Group 2, 8.7% of patients received dabigatran (110 mg/12 h), 3.3% dabigatran (150 mg/12 h), 11.4% rivaroxaban (20 mg/24 h), 4.4% rivaroxaban (15 mg/24 h), 7.4% apixaban (5 mg/12 h), and 7.4% apixaban (2.5 mg/12 h). Only 73% of patients who received a DAC took the recommended dose according to the summary of product characteristics; a reduced dose was used in 23%, and in 3%, a higher-than-recommended dose. Inappropriately reduced doses were 27% with dabigatran, 21% with rivaroxaban, and 31% with apixaban (Fig. 1). The treating physician selected the dose based on individualized assessment of thrombotic and hemorrhagic

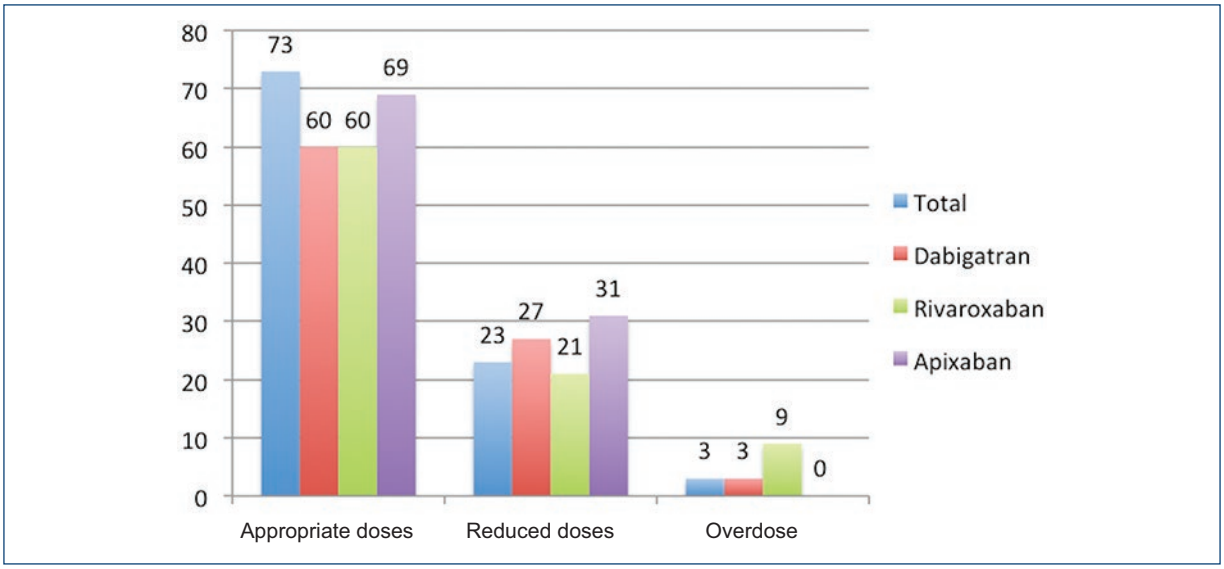


Figure 1. Direct anticoagulant doses used.

risk, and the main motivations that led to the use of a reduced dose were age, fragility, high bleeding risk, and kidney failure.

Patients in Group 3 (n = 30) did not receive treatment for the following reasons: fifteen patients (50%) had a low CHA_2DS_2-VASc score (11 subjects with CHA_2DS_2-VASc of 0 points, and four with CHA_2DS_2-VASc of 1 point[1] [one woman and three men who did not receive anticoagulation because they had a borderline indication]), four patients (13.3%) due to a history of major hemorrhagic episodes (one hemorrhagic stroke and three gastrointestinal bleeds), and 11 patients (37%) on their own decision not to receive anticoagulant treatment despite having a clinical indication.

Data from 273 patients were collected. Baseline characteristics of the patient populations of the VKA and DAC groups are presented in table 1. There were no differences between groups in terms of gender, dyslipidemia, history of ischemic heart disease, previous bleeding, or concomitant antiplatelet therapy, although, despite not reaching statistical significance, numerical differences were identified in baseline characteristics of the patients in the VKA and DAC groups. Patients in the VKA group were older, with a higher prevalence of hypertension, diabetes, chronic kidney failure, and heart failure in comparison with DAC group patients. In turn, thromboembolic risk scales mean values were significantly higher in the VKA group in comparison with the DAC group ($CHADS_2$, 2.24 ± 1.06 vs. 1.99 ± 1.20, p = 0.035; CHA_2DS_2-VASc, 3.84 ± 1.53 vs. 3.44 ± 1.67, p = 0.046) with a trend toward higher mean values also in the hemorrhagic risk scale, without statistical significance being reached (HASBLED, 2.31 ± 1.0 vs. 2.04 ± 1.08, p = 0.052). In turn, the type of AF was predominantly permanent in the VKA-treated group.

Cardiovascular events during follow-up

During a 24-month clinical follow-up, all-cause mortality was recorded in one patient in the DAC group and 16 patients in the VKA group (0.9 vs. 12.6%; HR, 0.88; 0.82-0.94; p < 0.01). Regarding mortality for cardiovascular causes, no events were identified in the DAC group and seven were observed in the VKA group (0.0 vs. 5.5%; HR, 0.94; 0.90-0.98; p = 0.01) (Table 2). In terms of safety and efficacy, no statistically significant differences were observed, although there were numerical differences between the DAC and VKA groups. There were three major ischemic events in the DAC group and one in the VKA group (2.6 vs. 0.8%; p = 0.27). No ischemic events were observed in the group that did not receive anticoagulation. As for hemorrhagic events, one major hemorrhagic event occurred in the DAC group and six in the VKA group (0.9 vs. 4.7%; p = 0.07); of the five patients treated with VKA who suffered lethal hemorrhagic events, three patients (60%) had an INR outside TTR when the event occurred. In the survival analysis, statistically

Table 1. AVK and ACD groups of baseline characteristics

	VKA (n = 127)	DAC (n = 116)	Sig.
Age (years)	75 ± 10	72 ± 10	0.01
Females	60 (47%)	59 (51%)	0.57
Smoking	20 (16%)	25 (22%)	0.34
Hypertension	107 (84%)	103 (89%)	0.30
Diabetes mellitus	43 (34%)	33 (28%)	0.36
Dyslipidemia	53 (42%)	61 (53%)	0.09
Kidney disease*	43 (34%)	26 (22%)	0.08
Heart failure	31 (24%)	20 (17%)	0.17
Previous stroke/TIA	14 (11%)	13 (12%)	0.63
Ischemic heart disease	25 (20%)	25 (22%)	0.72
Previous major bleeding	3 (2%)	6 (5%)	0.60
ASA treatment	22 (17%)	22 (19%)	0.72
SAME-TTR 0 1 2 3 4 5	1.5 ± 0.9 15 (12%) 56 (44%) 41 (32%) 14 (11%) 1 (1%) 0 (0%)	1.9 ± 1.1 8 (7%) 32 (28%) 40 (34%) 26 (22%) 6 (6%) 3 (3%)	<0.01
Number of daily tablets	8.85	8.14	0.541
LVEF Normal (> 55%) 45-54% 35-44% < 35%	 108 (85%) 6 (5%) 5 (4%) 8 (6%)	 104 (90%) 7 (5%) 2 (2%) 3 (3%)	 0.283
Type of atrial fibrillation Paroxysmal Persistent Permanent	 31 (24%) 16 (13%) 80 (63%)	 49 (42%) 35 (30%) 32 (28%)	<0.01
Thrombotic and hemorrhagic risk scales $CHADS_2$ CHA_2DS_2-VASc HASBLED	 2.24 ± 1.06 3.84 ± 1.53 2.31 ± 1.05	 1.99 ± 1.20 3.44 ± 1.67 2.04 ± 1.08	 0.035 0.046 0.052

*GFR values < 60 mL/min/1.73 m^2 and creatinine values > 1.3 mg/dL in males and > 1.2 mg/dL in females were considered kidney disease.
ASA: acetylsalicylic acid; TIA: transient ischemic attack; VKA: Vitamin K antagonist; DAC: direct anticoagulants.

significant differences were documented between both groups' curves (Fig. 2).

When the group of patients who received DAC was analyzed, there were no significant differences in events between different DACs or between different doses; however, there were too many subgroups with a very small sample size to show significant differences.

In the multivariate analysis, several MACE-predicting variables were recognized: VKA use ($p < 0.05$), age ($p < 0.05$), and CHA_2DS_2-VASc high scores (CHA_2DS_2-VASc, 3, and 4), which were significant, and thus they were introduced in the model represented in figure 3.

Anticoagulation control in patients on VKA

When analyzing the VKA group, mean time within direct TTR was 59.6 ± 25.8% and calculated using the

Table 2. Major adverse cardiovascular events during the 24-month follow-up

	VKA (n = 127)	DAC (n = 116)	Sig.	HR (95% CI)
CV mortality	7 (5.5%)	0 (0)	0.01	0.94; 0.90-0.98
Total mortality	16 (12.6%)	1 (0.9%)	< 0.01	0.88; 0.82-0.94
Thromboembolic events	1 (0.8%)	3 (2.6%)	0.27	1.02; 0.98-1.05
Hemorrhagic events	6 (4.7%)	1 (0.9%)	0.07	0.96; 0.92-1.00
Total MACE	17 (13.4%)	5 (4.3%)	0.01	0.90; 0.83-0.98

DAC: direct anticoagulants; VKA: Vitamin K antagonist; CV: cardiovascular; MACE: major adverse cardiovascular events; HR: hazard ratio; CI: confidence interval.

Overall comparisons			
	χ^2	df	Sig.
Log-rank (Mantel-Cox)	6.855	1	0.009

Test for equality of survival distributions for the different drug values.

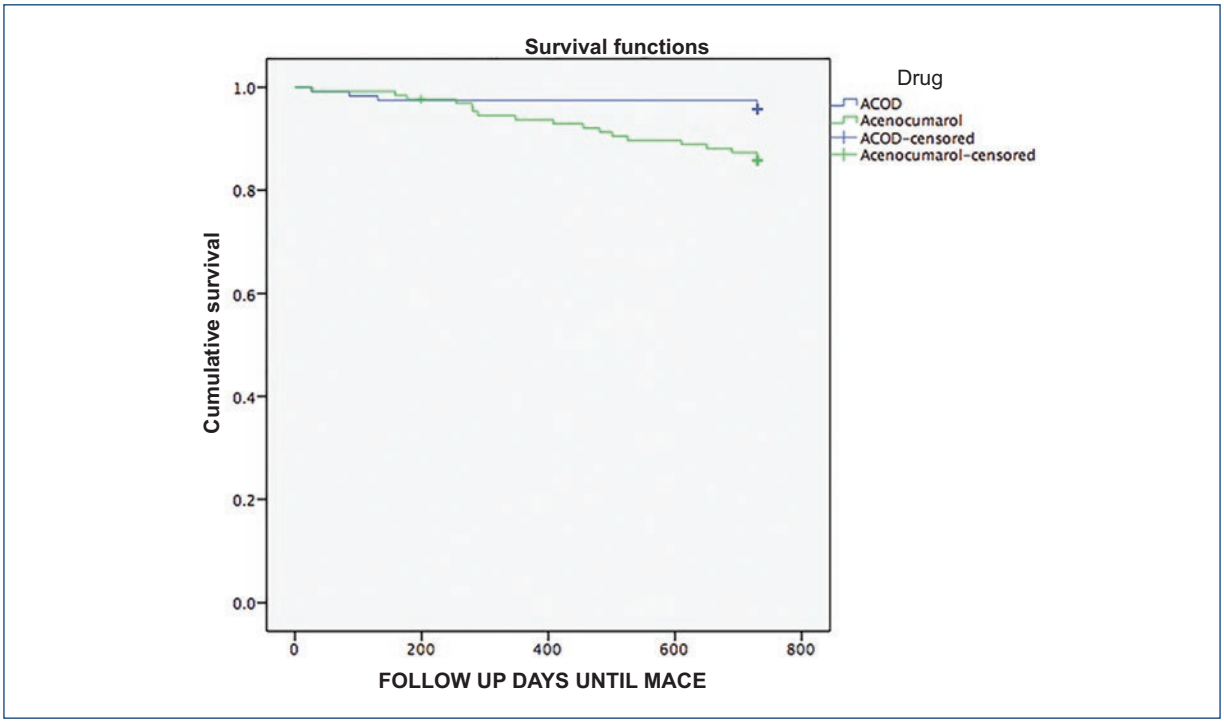
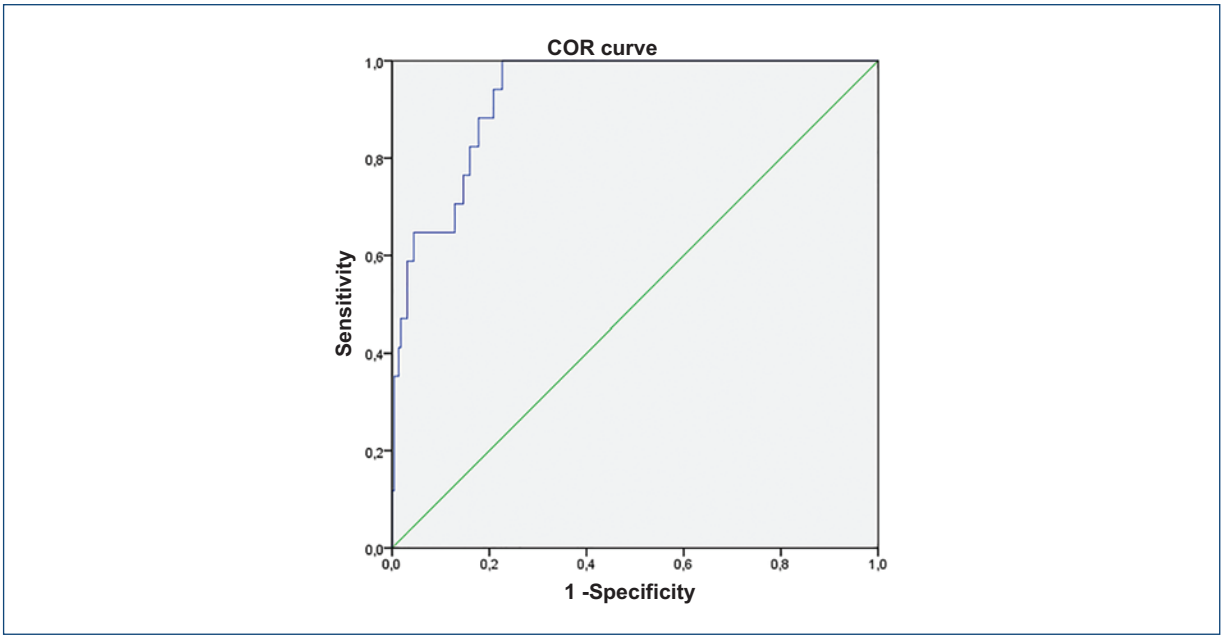


Figure 2. Major adverse cardiovascular events-free survival curves according to the anticoagulant treatment received.

Rosendaal formula, 62.1 ± 27.7%, with no differences deriving from the method used (p = 0.09). Anticoagulation was adequate according to the Rosendaal method in 55.1% of patients. Baseline characteristics of patients with poor control, according to the Rosendaal method, did not differ with regard to those who were controlled (TTR > 65%) included in the mean number of daily tablets for treatment in the SAME-TTR score or in

Variables in the equation								
	B	Standard error	Wald	df	Sig.	Exp (B) lower	95% CI for EXP (B)	
							Lower	Upper
Step 1*								
Age	0.169	0.046	13.610	1	0.000	1.184	1.082	1.295
Constant	-15.776	3.733	17.864	1	0.000	0.000		
Step 2**								
SINTROM (acenocoumarol) (1)	-2.576	1.053	5.989	1	0.014	0.076	0.010	0.599
Age	0.162	0.049	10.848	1	0.001	1.175	1.068	1.294
Constant	-14.655	3.993	13.469	1	0.000	0.000		
Step 3†								
SINTROM (acenocoumarol) (1)	-3.978	1.410	7.956	1	0.005	0.019	0.001	0.297
CHA_2DS_2-VASC			13.976	8	0.082			
CHA_2DS_2-VASC (1)	-17.581	15340.318	0.000	1	0.999	0.000	0.000	.
CHA_2DS_2-VASC (2)	-17.486	9167.695	0.000	1	0.998	0.000	0.000	.
CHA_2DS_2-VASC (3)	-3.123	2.308	1.830	1	0.176	0.044	0.000	4.062
CHA_2DS_2-VASC (4)	-4.629	2.318	3.988	1	0.046	0.010	0.000	0.918
CHA_2DS_2-VASC (5)	-4.930	2.178	5.123	1	0.024	0.007	0.000	0.516
CHA_2DS_2-VASC (6)	-4.024	2.175	3.422	1	0.064	0.018	0.000	1.271
CHA_2DS_2-VASC (7)	-2.927	2.176	1.809	1	0.179	0.054	0.001	3.813
CHA_2DS_2-VASC (8)	-0.096	2.201	0.002	1	0.965	0.909	0.012	67.877
AGE	0.204	0.070	8.499	1	0.004	1.226	1.069	1.407
Constant	-14.196	5.793	6.006	1	0.014	0.000		

*Variables specified in Step 1: age.
**Variables specified in Step 2: Sintrom (acenocoumarol).
†Variables specified in Step 3: CHA_2DS_2-VASC.



Area under the curve				
Test result variables: predicted probability				
Area	Standard error*	Asymptotic significance**	95% asymptotic confidence interval	
			Lower limit	Upper limit
0.929	0.022	0.000	0.886	0.973

*Under the nonparametric assumption.
**Null hypothesis: true area = 0.5.

Figure 3. Receiver operating characteristics curve related to the multivariate analysis of major adverse cardiovascular events predicting factors. Test for equality of survival distributions for the different range of degrees.

Table 3. Differences between VKA-anticoagulated patients by degree of control

	Good control (TTR > 60%) (n = 59)	Poor control (TTR < 60%) (n = 48)	Sig.
Age (years)	75 ± 10	74 ± 10	0.46
Females	28 (48%)	24 (50%)	0.79
Smoking	6 (10%)	8 (17%)	0.61
Hypertension	51 (86%)	38 (79%)	0.31
Diabetes mellitus	18 (31%)	14 (29%)	0.88
Dyslipidemia	21 (36%)	22 (46%)	0.28
Kidney disease*	23 (39%)	15 (30%)	0.18
Heart failure	16 (27%)	10 (21%)	0.45
Previous stroke/TIA	8 (14%)	3 (6%)	0.22
Ischemic heart disease	12 (20%)	9 (19%)	0.84
Previous major bleeding	1 (2%)	2 (4%)	0.47
Treatment with ASA	10 (17%)	11 (22%)	0.63
SAME-TTR 0 1 2 3 4	1.3 ± 0.8 9 (15%) 27 (46%) 18 (31%) 5 (9%) 0 (0%)	1.50 ± 0.9 5 (10%) 20 (42%) 18 (38%) 4 (8%) 1 (2%)	0.70
Number of daily tablets	8.83	9.00	0.12
LVEF Normal (> 55%) 45-54% 35-44% < 35%	 51 (86%) 2 (3%) 1 (2%) 5 (9%)	 39 (81%) 3 (6%) 4 (8%) 2 (4%)	0.30
Thrombotic and hemorrhagic risk scales $CHADS_2$ CHA_2DS_2-VASc HASBLED	 2.31 ± 0.95 3.98 ± 1.48 2.25 ± 1.03	 1.96 ± 0.97 3.56 ± 1.41 2.54 ± 1.12	 0.05 0.08 0.15
Major adverse cardiovascular events on 24-month follow-up CV mortality Overall mortality Thromboembolic events Hemorrhagic events Total MACE	 4 (6.8%) 9 (15.3%) 0 (0%) 1 (1.7%) 9 (15.3%)	 2 (4.2%) 4 (8.3%) 1 (2.1%) 2 (4.2%) 7 (14.6%)	 0.56 0.28 0.27 0.44 0.92

*GFR values < 60 mL/min/1.73 m^2 and creatinine values > 1.3 mg/dL in men and > 1.2 mg/dL in women were considered kidney disease.
ASA: acetylsalicylic acid; TIA: transient ischemic attack; VKA: Vitamin K antagonist; DAC: direct anticoagulants; CV: cardiovascular; MACE: major adverse cardiovascular events; TTR: time in TTR by Rosendaal method.

kidney function (Table 3). Although only in a non-significant numerical form, the out-of-range group had a higher mean score in the HAS-BLED scale (2.54 vs. 2.25; p = 0.16), a higher number of hemorrhagic (4.2 vs. 1.7%; p = 0.44), and major ischemic events (2.1 vs. 0%; p = 0.27), mortality due to cardiovascular causes (4.2 vs. 6.8%; p = 0.56) and all-cause mortality (8.3 vs. 15.3%; p = 0.27) were lower in this out of therapeutic range group (Table 3 and Fig. 4).

Discussion

The REACOH trial results reflect the treatment of NVAF in a large sample of anticoagulated patients

Overall comparisons			
	χ^2	df	Sig.
Log-rank (Mantel-Cox)	0.017	1	0.898

Test of equality of survival distributions for the different range of degrees.

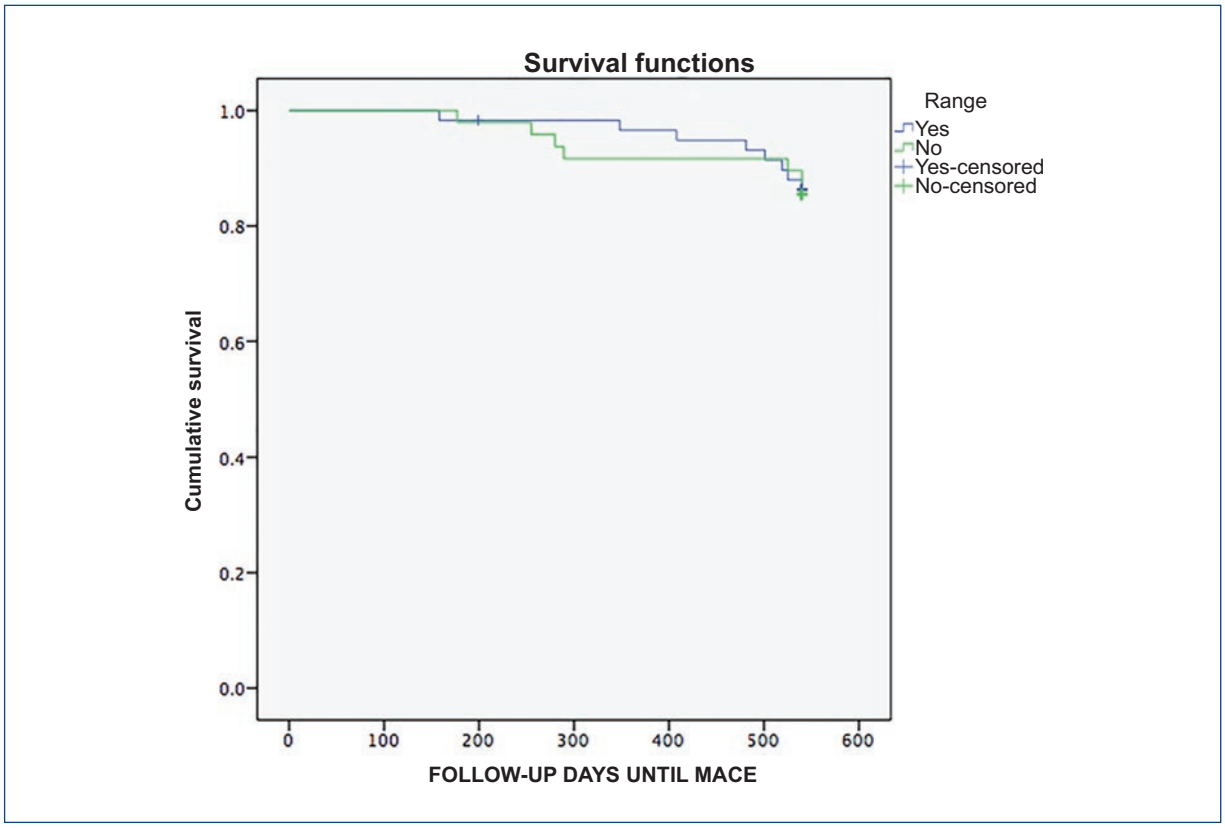


Figure 4. Vitamin K antagonists group major adverse cardiovascular effects-free survival curves by anticoagulation control degree.

representative of the population of the authors' hospital area served at the Department of Cardiology. It is important to note that surveillance of this work was highly meticulous and rigorous control was applied to guarantee the quality of the recorded data. Differences are shown in the profile of patients receiving anticoagulation with VKA or a DAC. The patients who received VKA were older and had more cardiovascular risk factors, including heart failure and kidney disease, which caused for patients who received a VKA to have higher scores in thrombotic and hemorrhagic risk scales in comparison with those who received a DAC (Table 1). The SAME-TTR scale score was higher in the DAC group, and it makes sense the choice of these drugs for a group that could be more difficult to maintain within TTR with VKA.

When analyzing the subgroup of patients on treatment with VKA (acenocoumarol in this case), the fact that almost half the patients lacked an adequate degree of anticoagulation control stands out. However, it is not surprising that those with poor control showed a non-significant tendency to exhibit more MACE during follow-up in comparison with the group that had adequate anticoagulation control. INR inadequate control is known to increase the risk of both stroke and hemorrhage[20]. Actually, it has been shown that in patients with NVAF and a $CHADS_2$ score $\geq$ 2 are treated with warfarin, in comparison with untreated

subjects, a significant improvement in the time to the occurrence of a stroke is observed only in subjects that reached an INR control > 70% of the time within TTR[21]. The degree of anticoagulation control, even in controlled clinical trials, reaches a maximum of 65-70%[20]; however, there is little evidence of control in a real-life population in our setting. The two largest registries in the authors' setting have documented poor anticoagulation control and have associated factors such as belonging to the female gender, elevated HASBLED score, diabetes mellitus, kidney disease, and hypertension, among others, with a poorer INR control[7,8]. Outside the authors' setting, multiple studies have associated various factors with poor INR control, even opposed to those found in this setting[20,22,23]. This study somehow elucidates the above, but no predicting factors of INR poor control have been identified (Table 3).

Cardiovascular mortality and overall mortality were significantly reduced in patients who received a DAC in comparison with those who received VKA. As previously mentioned, these differences could be partly justified due to the differences in age and cardiovascular risk factors between both groups. However, this benefit is mainly explained at the expense of a clear trend toward a reduction of hemorrhagic events in patients receiving DAC. On the other hand, in the study population, and similarly to the pivotal studies with DAC in the prevention of ischemic events, DACs have demonstrated similar efficacy to VKAs, with very low ischemic event rates in both subgroups. It should be noted that, in a high percentage of patients who received a DAC, doses were not appropriate, basically at the expense of underdosing; this fact is consistent with observations made in previous real-life studies[24] and could justify a numerical difference toward showing more events versus the VKA group.

The large difference in the number of major complications to the detriment of the VKA group stands out, which is something that in larger studies is apparently diluted[12-15]. Probably, the higher power of the study, thanks to a larger sample size, in addition to clinical differences and longer time within TTR in the VKA group, would have allowed bringing the number of complications between both groups closer together. With all these limitations, the authors consider that these differences, even if they were less marked, show a trend toward a safer and more predictable anticoagulation treatment with DACs.

Although scientific evidence in both randomized clinical trials and real-life studies show higher or equal safety of DACs in comparison with VKAs[15], the trend in this study was to administer VKAs in older patients with a larger number of comorbidities, although conceptually they might benefit more from the possible decrease in hemorrhagic risk that DACs could provide, especially considering that precisely in this population it is more difficult to achieve an adequate therapeutic control[20].

Limitations

The main limitation of this registry, i.e., its observational and non-controlled nature, introduces a possible selection bias that might affect its external validity. On the one hand, a clear limitation of the study is its small sample size, which particularly affects comparisons between different subgroups. The subgroup with edoxaban is not represented in the study for not being in the market when patient recruitment took place, and only acenocoumarol was used as a VKA drug. Finally, it should be mentioned that the comparisons of events between the VKA and DAC groups are limited given the different baseline characteristics in both groups and should be taken only as a reference. All this indicates that the results of this work should be considered only as hypothesis generators and that new studies are necessary to confirm the findings.

Conclusions

The results of this study indicate, first, that the profile of the anticoagulated patient for NVAF is different if treated with VKA or CAD. VKA-anticoagulated patients were almost half the time out of TTR. This fact, together with a higher risk profile in comparison with those treated with CAD, has been able to justify a MACE increase in this subgroup.

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Conflicts of interest

The head investigator has no conflicts of interest.

Ethical disclosures

Protection of people and animals. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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