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Quality of anticoagulation with vitamin K antagonists

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Abstract

Background. Vitamin K antagonists (VKA) have a narrow therapeutic range, and literature analysis reveals poor quality of anticoagulation control. We sought to assess the prevalence of poor anticoagulant control in patients under VKA treatment in the prevention of stroke for atrial fibrillation (AF).

Hypothesis.Control of anticoagulation with VKA is inadequate in a high percentage of patients with AF.

Methods.Patients with AF under VKA treatment were prospectively recruited in this observational registry. The sample comprised 948 patients. The estimated time spent in the therapeutic range (TTR) was calculated, and variables related with a TTR >65% were analyzed.

Results.Mean age was 73.8 ± 9.4 years, and 42.5% of the patients were women. Mean TTR was 63.77% ± 23.80% for the direct method and 60.27% ± 24.48% for the Rosendaal method. Prevalence of poor anticoagulation control was 54%. Variables associated with good anticoagulation control were university studies (odds ratio [OR]: 1.99, 95% confidence interval [CI]: 1.08-3.64), chronic hepatic disease (OR: 8.15, 95% CI: 1.57-42.24), low comorbidity expressed as Charlson index (OR: 0.87, 95% CI: 0.76-0.99), no previous cardiac disease (OR: 0.64, 95% CI: 0.41-0.98), lower risk of bleeding assessed as hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly age, and use of drugs or alcohol (HAS-BLED; OR: 0.81, 95% CI: 0.69-0.95), and lower heart rate (OR: 0.99, 95% CI: 0.98-0.99).

Conclusions.Patients who receive VKA to prevent stroke for AF spend less than half the time within therapeutic range.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and the major indication for long-term oral anticoagulation worldwide.[1] Vitamin K antagonists (VKAs), although no longer the only option, remain the pharmaceutical group more widely employed, due to their relatively low price and large amount of experience.

Coagulation status with VKAs needs to be monitored carefully to ensure maximal efficacy with minimal complication rates. The international normalized ratio (INR) is used to express the coagulation state, and several formulas have been proposed to assess the quality of anticoagulation. Among those formulas, the time in the therapeutic range (TTR) is the more extended and has proven to be a major determinant of the efficacy and safety of anticoagulation with VKAs.[2]

Literature analysis reveals poor quality of anticoagulation control with VKAs,[3-6] but it also shows important differences among countries.[2] In patients with suboptimal anticoagulation control with VKAs, strategies aimed to improve this control must be undertaken, including switching to a non–vitamin K antagonist oral anticoagulant (NOAC).

With this study we sought to assess the prevalence of poor anticoagulant control in patients under VKA treatment in the prevention of stroke for AF.

Methods

Patients

FANTASIIA is a multicenter observational study. Cardiologists, general practitioners, and internists participated in the study recruiting 20 consecutive patients with nonvalvular AF receiving uninterrupted anticoagulant treatment for stroke prevention for >6 months. By design, 16 patients had to receive VKAs and 4 NOACs. Patients were excluded for age <18 years, history of heart valve disorder (including prosthesis or moderate/severe valve disease), hospitalization at the moment, or if they were participating in a clinical trial. Patients unwilling or unable to provide written informed consent were also excluded. The study was conducted in Spain. The research protocol complied with the Declaration of Helsinki and was approved by the local ethics committee.

A total of 1290 patients were recruited; of those, 994 received VKAs (77.1%) and 296 received NOACs (22.9%). After the exclusion of 48 patients with incomplete registry of INR controls, the final sample for the analysis of quality of anticoagulation with VKAs consisted of 948 patients.

Coagulation status was determined by INR values of the 6 months previous to the study entry. The INR values were registered together with other clinical and analytical variables. Chronic kidney disease was defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2, and chronic hepatic disease was defined as having a past medical history of cirrhosis, hepatitis, any other chronic liver disorder, or persistent elevation of transaminases 3× the upper limit of normal. Stroke and hemorrhagic risks were calculated by means of the CHA_2DS_2-VASc[7] and hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly age, and use of drugs or alcohol (HAS-BLED) scores,[8] and the presence of comorbid diseases was assessed with the Charlson index.[9]

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International normalized ratio was determined monthly in the 6 months previous to the study entry. Direct method shows the proportion of INR controls within 2 and 3. The Rosendaal method uses linear interpolation to assign an INR value to each day between successive observed INR values.[10] The estimated time spent in the TTR was assessed by the Rosendaal method. Poor anticoagulation control was defined as an estimated TTR <65%.[11]

Statistical Analysis

All continuous variables showed normal distribution and are presented as mean ± SD. Discrete variables are presented as values (percentages). Baseline characteristics were compared between patients with adequate (TTR ≥65%) or inadequate (TTR <65%) VKA control. Logistic regression analyses were employed for univariate analyses and for multivariate adjustment. Multivariate models were performed including variables with recognized clinical relevance with VKA control and those with a *P* value <0.1 in the univariate analysis. Results are presented as odds ratios (ORs) and 95% confidence intervals (95% CIs). A 2-sided *P* value of <0.05 was considered to be significant for all analyses. All statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL).

Results

Mean age of the study population was 73.8 ± 9.4 years, and 42.5% of the patients were women. Clinical characteristics of the sample are depicted in Table 1.

Unadjusted analyses (Table 2) revealed higher control rates for higher education level; absence of cardiovascular risk factors: hypertension (78.52% TTR ≥65% vs 83.69% TTR <65%; OR: 0.71, *P* = 0.04), diabetes mellitus (27.25% TTR ≥65% vs 34.37% TTR <65%; OR: 0.72, *P* = 0.02), less comorbidity expressed as lower mean Charlson index (1.09 TTR ≥65% vs 1.30 TTR <65%; OR: 0.86, *P* = 0.01), lower thrombotic risk ($CHADS_2$: 2.22 TTR ≥65% vs 2.40 TTR <65%; OR: 0.89, *P* = 0.02) and hemorrhagic risk (HAS-BLED: 1.90 TTR ≥65% vs 2.08 TTR <65%; OR: 0.85, *P* = 0.01), and better glycemic control (glycemia: 107.05 TTR ≥65% vs 112.8 TTR <65%; OR: 0.99, *P* = 0.01, and glycated hemoglobin 6.10 TTR ≥65% vs 6.35 TTR <65%; OR: 0.86, *P* = 0.02). (For detailed pharmacological treatment, see Supporting Table in the online version of this article.)

Table 1. Baseline Characteristics of the Study Population Stratified by Time in the TTR

Variable	Total (N = 948)	TTR <65% (n = 515)	TTR ≥65% (n = 433)	*P* Value
Age, y	74.01	73.75	74.33	0.34
Female sex	43.25	42.33	44.34	0.53
Education				
Cannot write (Ref)	5.8	6.99	4.39	
Primary	70.15	71.26	68.82	0.14
Secondary	15.30	15.34	15.24	0.16
Higher education	3.06	2.52	3.70	0.07
University degree	5.70	3.88	7.85	0.00
HTN	81.33	83.69	78.52	0.04
Hyperlipidemia	54.85	53.40	56.58	0.33
DM	31.12	34.37	27.25	0.02
Smoking history				
Nonsmoker (Ref)	62.03	61.36	62.82	
Current smoker	4.43	5.63	3.00	0.06
Recent former smoker (<1 year)	2.22	2.33	2.08	0.76
Former smoker (<1 year)	31.33	30.68	32.10	0.88
Chronic pulmonary disease	16.67	17.09	16.17	0.70
Chronic kidney disease	21.10	22.52	19.40	0.24
Chronic hepatic disease	1.16	0.58	1.85	0.09
Active cancer	9.28	10.49	7.85	0.17
PAD	6.96	7.77	6.00	0.29
CVD				
None (Ref)	85.02	84.85	85.22	
Ischemic	9.92	9.51	10.39	0.70
Transient ischemic	4.32	4.85	3.70	0.40
Hemorrhagic	0.74	0.78	0.69	0.88
Systemic embolism	2.22	2.52	1.85	0.48
Charlson index	1.20	1.30	1.09	0.01
HF	31.75	34.37	28.64	0.06
CAD	20.25	20.78	19.63	0.66
DCM	13.29	13.20	13.39	0.93
Hypertrophic cardiomyopathy	3.06	3.11	3.00	0.93
LVH	17.19	16.70	17.78	0.66
Recent bleeding (6 months)	2.53	3.30	1.62	0.11
Type of AF				
Paroxysmal (Ref)	26.9	26.80	27.02	
Persistent	17.72	18.25	17.09	0.71
Long-term persistent	3.90	3.69	4.16	0.75
Permanent	51.48	51.26	51.73	1.00
EHRA functional class				
I (Ref)	38.61	40.39	36.49	
II	52.32	49.71	55.43	0.13
III	8.65	9.51	7.62	0.63
IV	0.42	0.39	0.46	0.78
CHADS2 score, mean	2.32	2.40	2.22	0.02
CHA2DS2-VASc score, mean	3.79	3.87	3.70	0.10
HAS-BLED score, mean	1.99	2.08	1.90	0.01
Rhythm at inclusion				
Sinus (Ref)	30.80	28.54	33.49	
AF	61.81	63.30	60.05	0.14
Pacemaker	6.54	7.18	5.77	0.18
Other	0.84	0.97	0.69	0.50
Conduction disturbances				
None (Ref)	77.34	80.59	73.47	
AV block	3.54	4.36	2.58	0.25
RBBB	10.31	7.52	13.62	0.00
LBBB	8.81	7.52	10.33	0.08
LVEF, %, mean	58.29	58.09	58.53	0.59
Hg, g/dL, mean	13.66	13.69	13.63	0.64
sCr, mg/dL, mean	1.07	1.09	1.06	0.33
eGFR, mL/min/1.73 m2, mean	65.49	65.75	65.17	0.70
Glycemia, mg/dL, mean	110.18	112.81	107.05	0.01
HbA1c, %, mean	6.23	6.35	6.10	0.02

Abbreviations: AF, atrial fibrillation; AV block, atrioventricular block; CAD, coronary artery disease; CI, confidence interval; CVD, cerebrovascular disease; DCM, dilated cardiomyopathy; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; EHRA, European Heart Rhythm Association; HbA_{1c}, glycated hemoglobin; HF, heart failure; Hg, hemoglobin; HTN, hypertension; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; RBBB, right bundle branch block; Ref, reference category; PAD, peripheral artery disease; sCr, serum creatinine; TTR, time in the therapeutic range.
Data are presented as % unless otherwise indicated.

Table 1. Univariate Comparison of the Population With Effect of Each Variable on the Quality of Anticoagulation

Variable	TTR < 65% (n = 515)	TTR ≥65%(n = 433)	OR	95% CI	*P* Value
Age, y	73.75	74.33	1.01	0.99-1.02	0.34
Female sex	42.33	44.34	1.09	0.84-1.40	0.53
Education					
Cannot write (Ref)	6.99	4.39			
Primary	71.26	68.82	1.54	0.86-2.74	0.14
Secondary	15.34	15.24	1.58	0.83-3.02	0.16
Higher education	2.52	3.70	2.33	0.93-5.85	0.07
University degree	3.88	7.85	3.22	1.47-7.05	0.00
HTN	83.69	78.52	0.71	0.51-0.99	0.04
Hyperlipidemia	53.40	56.58	1.14	0.88-1.47	0.33
DM	34.37	27.25	0.72	0.54-0.95	0.02
Smoking history					
Nonsmoker (Ref)	61.36	62.82			
Current smoker	5.63	3.00	0.52	0.27-1.02	0.06
Recent former smoker (<1 year)	2.33	2.08	0.87	0.36-2.10	0.76
Former smoker (<1 year)	30.68	32.10	1.02	0.77-1.35	0.88
Chronic pulmonary disease	17.09	16.17	0.94	0.66-1.32	0.70
Chronic kidney disease	22.52	19.40	0.83	0.60-1.13	0.24
Chronic hepatic disease	0.58	1.85	3.21	0.85-12.19	0.09
Active cancer	10.49	7.85	0.73	0.46-1.14	0.17
PAD	7.77	6.00	0.76	0.45-1.26	0.29
CVD					
None (Ref)	84.85	85.22			
Ischemic	9.51	10.39	1.09	0.71-1.67	0.70
Transient ischemic	4.85	3.70	0.76	0.40-1.44	0.40
Hemorrhagic	0.78	0.69	0.89	0.20-3.99	0.88
Systemic embolism	2.52	1.85	0.73	0.30-1.77	0.48
Charlson index	1.30	1.09	0.86	0.77-0.96	0.01
HF	34.37	28.64	0.77	0.58-1.01	0.06
CAD	20.78	19.63	0.93	0.68-1.28	0.66
DCM	13.20	13.39	1.02	0.70-1.48	0.93
Hypertrophic cardiomyopathy	3.11	3.00	0.97	0.46-2.03	0.93
LVH	16.70	17.78	1.08	0.77-1.51	0.66
Recent bleeding (6 months)	3.30	1.62	0.48	0.20-1.17	0.11
Type of AF					
Paroxysmal (Ref)	26.80	27.02			
Persistent	18.25	17.09	0.93	0.63-1.37	0.71
Long-term persistent	3.69	4.16	1.12	0.56-2.23	0.75
Permanent	51.26	51.73	1.00	0.74-1.36	1.00
EHRA functional class					
I (Ref)	40.39	36.49			
II	49.71	55.43	1.23	0.94-1.62	0.13
III	9.51	7.62	0.89	0.54-1.44	0.63
IV	0.39	0.46	1.32	0.18-9.45	0.78
CHADS2 score, mean	2.40	2.22	0.89	0.80-0.98	0.02
CHA2DS2-VASc score, mean	3.87	3.70	0.93	0.86-1.01	0.10
HAS-BLED score, mean	2.08	1.90	0.85	0.75-0.96	0.01
Rhythm at inclusion					
Sinus (Ref)	28.54	33.49			
AF	63.30	60.05	0.81	0.61-1.07	0.14
Pacemaker	7.18	5.77	0.68	0.39-1.20	0.18
Other	0.97	0.69	0.61	0.14-2.59	0.50
Conduction disturbances					
None (Ref)	80.59	73.47			
AV block	4.36	2.58	0.65	0.31-1.36	0.25
RBBB	7.52	13.62	1.98	1.28-3.07	0.00
LBBB	7.52	10.33	1.51	0.95-2.38	0.08
LVEF, %, mean	58.09	58.53	1.00	0.99-1.02	0.59
Hg, g/dL, mean	13.69	13.63	0.98	0.91-1.06	0.64
sCr, mg/dL, mean	1.09	1.06	0.87	0.66-1.15	0.33
eGFR, mL/min/1.73 m2, mean	65.75	65.17	1.00	0.99-1.00	0.70
Glycemia, mg/dL, mean	112.81	107.05	0.99	0.99-1.00	0.01
HbA1c, %, mean	6.35	6.10	0.86	0.76-0.98	0.02

Abbreviations: AF, atrial fibrillation; AV block, atrioventricular block; CAD, coronary artery disease; CI, confidence interval; CVD, cerebrovascular disease; DCM, dilated cardiomyopathy; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; EHRA, European Heart Rhythm Association; HbA1c, glycated hemoglobin; HF, heart failure; Hg, hemoglobin; HTN, hypertension; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; RBBB, right bundle branch block; Ref, reference category; PAD, peripheral artery disease; sCr, serum creatinine; TTR, time in the therapeutic range.
An OR >1 indicates that the presence of the variable increases the likelihood of good anticoagulation control, assessed by TTR ≥65%.

Prevalence of poor anticoagulation control was 54% (515 patients with TTR <65%). Mean TTR was 63.77% ± 23.80% for the direct method and 60.27% ± 24.48% for the Rosendaal method. Each patient was 90.41 ± 36.72 days within the therapeutic range out of the 180 days of registry. A total of 4.7% of the study population was between 0 and 30 days within INR range 2–3; 17.3% between 30 and 60 days; 26.4% between 60 and 90 days; 21% between 90 and 120 days; and 21% >120 days. None of the INR values were within range in 1.3% of the sample; 4.4% had only 1 determination within range; 12.1% had 2; 22.9% had 3; 24.7% had 4; 21.7% had 5; and 13.5% of patients had all their INR measurements between 2 and 3.

After multivariate adjustment (Table 3), variables associated with good anticoagulation control were university studies (OR: 1.99, 95% CI: 1.08-3.64), chronic hepatic disease (OR: 8.15, 95% CI: 1.57-42.24), low comorbidity expressed as Charlson index (OR: 0.87, 95% CI: 0.76-0.99), no previous cardiac disease (OR: 0.64, 95% CI: 0.41-0.98), lower risk of bleeding assessed as HAS-BLED (OR: 0.81, 95% CI: 0.69-0.95), and lower heart rate (OR: 0.99, 95% CI: 0.98-0.99).

Table 3. Multivariable Analysis, Variables Associated With TTR ≥65%

Variable	OR	95% CI	*P* Value
University studies	1.99	1.08-3.64	0.03
Chronic hepatic disease	8.15	1.57-42.24	0.01
Charlson index	0.87	0.76-0.99	0.03
No previous cardiac disease	0.64	0.41-0.98	0.04
HAS-BLED	0.81	0.69-0.95	0.01
Heart rate (bpm)	0.99	0.98-1.00	0.03

Abbreviations: CI, confidence interval; ECG, electrocardiogram; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly age, and use of drugs or alcohol; INR, international normalized ratio; OR, odds ratio; TTR, time in the therapeutic range.
Model adjusted by age, sex, kidney disease, ECG conduction disturbances, previous ablation, and diuretic treatment.

Discussion

Our study shows a rate of inadequate control with AVKs of 54%, and 46% of the patients spent more than half the time outside the therapeutic range.

The poor control of anticoagulation is of concern. Prognosis of patients under anticoagulant treatment has been proven to differ significantly according to INR control,[3, 12, 13] and some strategies are now available to improve the quality of oral anticoagulation. Those strategies include the use of computer-assisted dosing tools, self-monitoring, improving patient compliance, use of dedicated anticoagulation clinics, genotype-guided dosing, and switch to NOACs.[3, 14, 15] Causes of the low achievement of adequate anticoagulation are multiple, including underuse of strategies designed to improve control, therapeutic inertia, comorbidities, and socioeconomical variables that preclude the use of NOACs. Efforts have been made to increase the prescription of anticoagulation for patients with AF in accordance with international guidelines,[16, 17] but the quality of this anticoagulation has to be evaluated.

A large observational study involving 6250 patients from France, Germany, Italy, and the United Kingdom treated with VKAs and with available INR has recently been published. Good VKA control was defined as TTR >70%; the rates of inadequate control found were 52% in France, 56% in Germany, 54% in Italy, and 45% in the United Kingdom.[18] A pooled analysis of AF studies published between 1990 and 2013 showed a mean TTR of 61% and 56% of INR measures within therapeutic range,[2] whereas an older meta-analysis including studies performed in the United States showed a mean TTR of 57% and 51% of time within range.[3] A more recent study showed TTR values between 70.3% and 81.4% among Western European countries.[19]

In our study, the variables associated with adequate VKA adjustment were higher education, expressed as having a university degree; low comorbidity, expressed as low Charlson index; no previous cardiac disease, lower risk of bleeding, chronic hepatic disease, and lower heart rate. Classic studies evaluating compliance with anticoagulants revealed that younger age, male sex, or nonwhite race were factors associated with lack of compliance.[20] A more recent study revealed poor compliance with anticoagulants in patients with higher educational level, current employment, and lower scores on mental

health or cognitive functioning.[21] This apparent controversy was explained by the decreased trust in physicians among more educated subjects, whereas poor cognition has been associated with worse treatment adherence also in other areas.[22] In our study, having a university degree was associated with adequate anticoagulation control. We believe that higher education helps patients to understand the importance of anticoagulant treatment adherence. The association we have found between education and control is not limited to university studies; on the contrary, we can see a progressive increase in the OR for adequate control for progressively higher levels of education (Table 2).

The explanation of how chronic liver disease and lower heart rate are associated with adequate VKA control is unclear. We speculate that both patients and physicians are more careful when anticoagulating patients with chronic liver disease. Patients with higher heart rate are more prone to heart failure decompensation and to receive chronotropic/antiarrhythmic drugs, 2 factors that may interfere with VKA anticoagulation. These hypotheses need to be confirmed in future studies.

Study Limitations

We must acknowledge several study limitations. First, ours is an observational, transversal study. Second, we do not know which patients had their INR controls performed by general practitioners, cardiologists, hematologists, or anticoagulation clinics, or by self-monitoring. Duration of the arrhythmia and echocardiographic variables other than left ventricular ejection fraction were not available, and thus these data have not been analyzed. The results we present are representative of Spain, but previous reports have shown that in Spain INR control is equal or superior to that in other Western countries such as Italy, France, the United States, or Canada.[23] Another peculiarity of our study is that in Spain the predominant VKA is acenocoumarol, as opposed to most Western countries, where warfarin is mainly used.

Conclusion

Patients who receive VKAs to prevent stroke for AF spend <50% of the time within therapeutic range. Efforts must be made to improve efficacy and security of chronic anticoagulation.

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