ORIGINAL ARTICLE

Nontherapeutic international normalized ratio results in hospital emergency patients on vitamin K antagonists: prevalence and associated factors

Xavier López Altimiras[1], Emili Gené Tous[2,3,4], Antonio De Giorgi[5], Andrés Gadea Polo[2,3], Raquel Martín Horcajo[1], Sònia Jiménez Hernández[6]

Aims. To determine the prevalence of international normalized ratio (INR) findings outside the normal range in hospital emergency department patients on vitamin K antagonists (VKAs). To identify factors associated with abnormal anticoagulant levels in these patients.

Methods. Observational, cross-sectional, multicentric study in 4 hospital emergency departments. We included a convenience sample of patients on VKA treatment for whom INR levels were on record and who had sought emergency care for complications unrelated to anticoagulant treatment.

Results. We included 376 patients with a mean (SD) age of 76.8 (10.1) years; 50.3% were women and 86.7% had atrial fibrillation. We found that 60.4% (95% CI, 55.3%–65.2%) had INRs outside the reference range. Multivariate analysis showed that changes in the patients' other long-term medications were independently associated with nontherapeutic INR results (odds ratio, 1.6; 95% CI, 1.02–2.79; *P*=.035).

Conclusions. Over 60% of patients on VKA treatment who come to hospital emergency departments with complaints unrelated to anticoagulant therapy have INR values outside the normal range. Changes in a patient's usual medications are significantly associated with nontherapeutic INR findings.

Keywords: Emergency health services. Treatment appropriateness. Oral anticoagulants. Atrial fibrillation.

Prevalencia y factores asociados a un International Normalized Ratio (INR) fuera de rango en pacientes en tratamiento con antivitamina K atendidos en servicios de urgencias hospitalarios

Objetivos. Determinar la prevalencia de un *International Normalized Ratio* (INR) fuera de rango entre los pacientes que acuden a los servicios de urgencias hospitalarios (SUH) y se encuentran en tratamiento con fármacos antivitamina K (AVK). Identificar los factores que se asocian con unos valores inadecuados de anticoagulación en estos pacientes.

Método. Estudio multicéntrico, observacional y transversal en cuatro SUH. Se incluyeron pacientes en tratamiento con AVK a los que se les realizó una analítica con determinación de INR, que no acudían por complicaciones asociadas al tratamiento anticoagulante. La inclusión se realizó mediante un muestreo de oportunidad.

Resultados. Se incluyeron en el estudio un total de 376 pacientes. Edad media de 76,8 (10,1) años, 50,3% fueron mujeres. El 86,7% de los pacientes presentaban fibrilación auricular. El 60,4% (IC 95%: 55,3%-65,2%) de los pacientes tuvieron un INR fuera de rango. El análisis multivariado demostró que los cambios en los medicamentos habituales con *odss ratio* (OR) de 1,6 (IC 95%: 1,02-2,79; p = 0,035) se asociaron de forma independiente a la presencia de un INR fuera de rango.

Conclusiones. El 60,4% de los pacientes en tratamiento con AVK que acuden a un SUH sin complicaciones asociadas al tratamiento anticoagulante presenta un INR fuera de rango. Los cambios en el tratamiento habitual del paciente se relacionaron significativamente con un INR fuera de rango.

Palabras clave: Emergencias. Adecuación. Anticoagulación oral. Fibrilación auricular.

Authors affiliation:
[1]Servicio de Urgencias, Hospital Universitario de Mollet, Barcelona, Spain.
[2]Servei d'Urgències Parc Taulí Hospital Universitari. Institut d'Investigació i Innovació Parc Taulí I3PT.
[3]Departament de Medicina Universitat Internacional de Catalunya.
[4]Centro de Investigación Biomédica en Red enfermedades hepáticas y digestivas (CIBERehd).
[5]Departamento de Medicina Universitat Interncional de Catalunya. Servicio de Urgencias, Quirónsalud Hospital Universitario General de Cataluña. Barcelona, Spain.
[6]Área de Urgencias, Hospital Clínic. Grupo UPyP, IDIBAPS. Barcelona, Spain.

Contribution of authors:
All authors have confirmed their authorship in the author's responsibilities documents publication agreement and assignment of rights to EMERGENCIAS.

Corresponding author:
Emili Gene Tous.
Servei de Urgències Parc Taulí Sabadell. Hospital Universitari Parc Tauli 1. 08208 Sabadell Barcelona, Spain

E-mail:
egene@tauli.cat

Article information:
Received: 7-10-2016
Accepted: 25-11-2016
Online: 24-1-2017

Editor in charge:
Agustín Julián Jiménez, MD, PhD.

Introduction

The antivitamin K (AVK), warfarin and acenocoumarol in Spain have represented the most common oral anticoagulants and are part of the therapeutic arsenal for the prevention and treatment of venous and arterial thromboembolic disease for many decades. Its mechanism of action is based on interfering with the cyclic interconversion of vitamin K and its epoxide, preventing the carboxylation of glutamate residues from vitamin K-dependent (II, VII, IX and X)[1] coagulation factors.

More than 200 drugs interact with the AVK through multiple mechanisms, enhancing or inhibiting its effect. This interaction leads to an increased risk of bleeding or

thrombosis. Several dietary and environmental factors also exert marked effects on AVK[2] anticoagulation. In addition, there are different clinical conditions that are associated with INR instability: hepatic dysfunction, hypermetabolic states, heart failure or renal failure[3].

The effectiveness and safety of the treatment depends on the adequate control of the degree of anticoagulation. For this reason, the International Normalized Ratio (INR) should be maintained between 2 and 3 for most indications. Therefore, the therapeutic window for AVK is quite narrow, and this is its main limitation in clinical practice. Patients with INR, usually in range, have significantly fewer haemorrhagic and/or thromboembolic events and can be controlled at longer time intervals[3]. Nonadherence to AVK treatment is one of the main causes of out-of-range INR[4].

The control of INR in patients treated with AVK can be performed in specialized units of haematology, usually in hospital settings, or by GPs in primary care centres. In addition, the self-control modality has also recently been introduced[5,6]. Some studies indicate that control in specialized units may be associated with a longer INR time in range[7,8].

Despite the large number of patients being treated with AVK and the numerous studies performed to evaluate the adequacy of the treatment according to the INR range, it is noteworthy that the vast majority of these studies have been performed at programmed control visits at primary care centres (PCC) or in specialized units of hematology[9]. In contrast, there is very little data on the adequacy of INR in patients treated with AVK who are treated in hospital emergency services (HES)[10]. Patients attending the HES represent a sample of the population with particularly interesting epidemiological characteristics, because they can be a good approximation to the situation of actual clinical practice, much more so than patients included in clinical trials and studies performed in specialized consultations. These patients present acute clinical conditions that are almost always superimposed on chronic diseases. Therefore, assessing the adequacy of AVK treatment in this population can be a valuable source of information. In addition, the study of demographic and social factors, drugs, comorbidities, factors related to the characteristics of the use of VKA and to the stay in HES may allow to identify their potential to alter the degree of adequacy of INR.

Therefore, the main objective of the present study is to determine the prevalence of out-of-range INR among patients who come to the HES for any reason and are on treatment with AVK drugs. The secondary objective is to identify factors that may be associated with the presence of an out-of-range INR.

Method

Multicentre, observational and cross-sectional study in four HES from the province of Barcelona. We included patients on treatment with AVK who attended the participating HES and who underwent an INR determination. The study period was one year, starting on January 1, 2013. The inclusion was made through an opportunity sampling that depended on the working day of the principal investigator of each center. Since this is a prospective study we chose this type of sampling to ensure the reliability of the observers. Patients in whom the reason for consultation was due to thrombotic and/or haemorrhagic complications were excluded.

For the calculation of the sample size, a reference population was assumed for the four-participating hospital centres of approximately 1.5 million people, of whom 1.5% could be on anticoagulant treatment with AVK. Given that previous studies have indicated that 60% of patients receiving AVK come to the HES with an out-of-range INR, with a 5% confidence interval and a 95% confidence level, we calculated a sample size of 375 individuals.

The main variable was the INR value, in range or out of therapeutic range. An INR in rank was considered when its value was between 2 and 3, except for the patients with mechanical valvular prosthesis for whom a value between 2.5 and 3.5 was considered in the range. As independent variables, variables such as age, sex, body mass index (BMI), variables of comorbidity (Barthel and Charlson index, number of common medications, number of admissions and emergency visits in the last year, (variables such as anticoagulation indication, duration of treatment, place of control of oral anticoagulant treatment and date of last control), variables related to the attention in HEMs of priority according to the Andorran Model of Triage -MAT- and destination after the visit in the HES). In addition, we assessed the withdrawal or introduction of new drugs since the last INR control. Obesity was defined when the body mass index (BMI) was equal to or greater than 30 kg/m^2, a severe dependence such as a Barthel score lower than 45, high comorbidity as a Charlson score equal to or greater than 3 and polymerization in those patients treated with five or more drugs.

The data collection was done through a direct interview to the patient or to the relatives in case the patient's cognitive deterioration prevented it. In addition, a review of the report of care in the HES and of the patient's medical history was performed.

For the statistical analysis, the categorical variables are expressed as percentages and the continuous variables as mean and standard deviation (SD). A univariate analysis was performed for the description of the population and the percentage of patients in the therapeutic range. For the comparison of the categorical variables, the chi squared test or the Fisher exact test was used. For the comparison of the quantitative variables, the Student's t test or the Mann-Whitney U test was used, depending on whether or not the variables followed a normal distribution.

The associations between the dependent variable and the independent variables were estimated using the odds ratio (OR) with their 95% confidence intervals (CI). To know the variables that predicted that a patient

taking AVK presented an INR outside the therapeutic range, and thus to rule out confounding factors, a multivariate study was performed through a multiple logistic regression model with successive steps forward, including all the independent variables that in the univariate analysis had a $p < 0.1$. Statistical analysis was performed using the statistical package SPSS 18.0.

The study was approved by the Ethics Committees of the four participating centres (CEIC Code 20123008). The study (ALT-AVK-2012-01) was classified by the Spanish Agency of Medicines and Sanitary Products as a Post-authorization Study with other designs than the prospective follow-up "EPA-OD". All patients included in the study signed informed consent.

Results

A total of 376 patients were included in the study. The mean age was 76.8 (SD: 10.1) years. 50.3% were women and 26.8% were obese (BMI > 30). The description of the biodemographic and comorbidity variables can be seen in Table 1. Eighty-seven percent of patients included in the study had atrial fibrillation (AF), which was the main indication of AVK treatment, and 75.8 % Hypertension (HT) (Table 1). Most patients underwent AVK treatment in a PCC (68.4%) and 75.5% were assigned a MAT triage priority of 1, 2 or 3 (Table 2).

From all patients on AVK who attended HES, 60.4% (95% CI: 55.3% -65.2%) had an out-of-range INR, 47.6% above and 52.4% under. Univariate analysis showed that patients with out-of-range INR were more frequently admitted or kept under observation (22% vs 17.4%, p = 0.02). In addition, patients with out-of-range INR had a tendency to be younger (75.9 years vs 78.0 years, p = 0.052), to present a cerebrovascular accident (stroke) as a pathological antecedent (14.5 % versus 8%, p = 0.058), more frequently since the last INR control, a change in the usual medications by introduction or withdrawal (31.7% vs 20.1%, p = 0.06) And were prosthetic valve carriers (22% vs. 14.7%, p = 0.08). Severe dependence, high comorbidity, polymedication, different pathological antecedents, indication of anticoagulant treatment or place of control were not significantly associated with an out-of-range INR (Tables 1 and 2).

The multivariate analysis showed that changes in the usual drugs by introduction or withdrawal, with OR 1.6 (95% CI 1.02-2.79, p = 0.035), are independently associated with the presence of an out-of-range INR in patients who seek treatment with HVA and who do not consult for complications associated with such treatment.

Discussion

The results of the study show, as well as many other studies in Spain[9,11-13] and in other European countries, that a very high percentage of patients receiving AVK

Table 1. Biodemographic characteristics, comorbidity and pathological antecedents

	Total 376 (100%) n (%)	INR in range 149 (39.6%) n (%)	INR out of range 227 (60.4%) n (%)	P value
Biodemographic variables				
Age in years [average (DE)]	76.8 (10.1)	78 (8.7)	75.9 (10.9)	0.052
Sex woman	189 (50.3)	76 (51)	113 (49.8)	0.82
BMI value in kg / m^2 [mean (SD)]	27.8 (5.1)	27.4 (4.9)	28 (5.2)	0.28
BMI > 30 [n (%)]	99 (26.8)	38 (25.5)	61 (26.8)	0.84
Comorbidity variables				
Score I. Barthel [media (DE)]	84.7 (22.5)	85.8 (22.5)	84 (26.2)	0.50
Score I Chalson [media (DE)]	4.25 (2.1)	4.07 (1.9)	4.4 (2.2)	0.19
Serious dependency	36 (9.6)	11 (7.4)	25 (11)	0.24
Severe comorbidity	300 (79.8)	121 (81.2)	179 (78.8)	0.10
Polypharmacy	322 (85.6)	126 (84.5)	196 (86.3)	0.63
Admitted < 1 year	165 (43.9)	55 (36.9)	110 (48.5)	0.28
Pathological antecedents				
Atrial fibrillation	326 (86.7)	133 (89.2)	193 (85)	0.23
Arterial hypertension	285 (75.8)	114 (76.5)	171 (75.3)	0.79
Chronic renal failure	77 (20.5)	25 (16.8)	52 (22.9)	0.15
Anemia	59 (15.7)	26 (17.4)	33 (14.5)	0.45
Hypercholesterolemia	131 (34.8)	53 (35.5)	78 (34.3)	0.81
Heart failure	170 (45.2)	67 (44.9)	103 (45.3)	0.93
Diabetes mellitus	119 (31.6)	49 (32.8)	70 (30.8)	0.67
Chronic obstructive pulmonary disease	91 (24.2)	36 (24.1)	55 (24.2)	0.98
Ischemic heart disease	83 (22.1)	26 (17.4)	57 (25.1)	0.08
Stroke	45 (12)	12 (8)	33 (14.5)	0.058
Hypothyroidism	30 (8)	12 (8)	18 (7.9)	0.96
Dementia	28 (7.4)	9 (6)	19 (8.3)	0.40
Depression	36 (9.6)	15 (10)	21 (9.2)	0.79
Chronic Enolism	11 (2.9)	6 (4)	5 (2.2)	0.30
Smoking	18 (4.8)	7 (4.6)	11 (4.8)	0.95

INR: International Normalized Ratio; BMI: body mass index.

Table 2. Variables related to the characteristics of use of the antivitamin K and the care in the emergency room

	Total N = 376 (100%) n (%)	INR in range N = 149 (39.6%) n (%)	Out-of-range INR N = 227 (60.4%) n (%)	P Value
Features use AVK				
Indication				
Atrial fibrillation	326 (86.7)	133 (89.2)	193 (85)	0.23
Venous thromboembolic disease	40 (10.6)	16 (10.7)	24 (10.5)	0.96
Prosthetic valve	72 (19.1)	22 (14.7)	50 (22.0)	0.08
Control place				
Primary Care Center	257 (68.4)	109 (73.1)	148 (65.1)	0.1
Clinical hemostasis	119 (31.6)	40 (26.8)	79 (34.8)	0.1
Duration of oral treatment				
> 1 year	264 (74.6)	108 (72.4)	156 (68.7)	0.47
Average years [average (DE)]	6.2 (6.3)	6.7 (6.7)	5.9 (5.9)	0.21
Last check in less than 12 days	182 (50.3)	73 (49.9)	109 (48.0)	0.89
Modification of usual treatment				0.06
Yes	102 (27.1)	30 (20.1)	72 (31.7)	
Introduction drugs	83 (22.1)	25 (16.7)	58 (25.5)	
Drug withdrawal	11 (2.9)	4 (2.6)	7 (3)	
Features attention in the emergency room				
Level MAT				0.18
1 + 2 + 3	289 (75.5)	107 (71.8)	176 (77.5)	
4 + 5	92 (24.5)	42 (28.1)	50 (22)	
Destination from first visit				0.02
High	187 (49.7)	87 (58.3)	100 (44)	
Observation	113 (30.1)	36 (24.1)	77 (33.9)	
In hospital	76 (20.2)	26 (17.4)	50 (22)	
Deaths	0 (0)	0 (0)	0 (0)	

INR: International Normalized Ratio; MAT: Andorran Triage Model.

are out of range. However, this is the first study to be done in the field of HES and in our environment. In addition, in our case, all patients treated with AVK were included, regardless of their indication, unlike other studies in which only patients with non-valvular AF were included.

In most studies, between 40% and 60% of patients are out of range. In this study, the percentage was 60.4%. It is a fact that out-of-range INR is a powerful predictor of thrombotic and haemorrhagic complications[14-17]. Therefore, the detection of these patients in HES by performing an INR determination would allow initiating corrective and preventive measures.

Our study, carried out in the HES of four hospitals, one located in Barcelona city and the remaining three in the province of Barcelona, analyses a wide sample of population, with an area of influence of the four participating hospitals of 1,440,000 inhabitants. No differences have been found in the results obtained between the centres.

The inclusion of patients in a situation of daily clinical practice allows to obtain data in the "real life", which gives them a special interest. There are several studies that verify that the records made in situations of clinical practice obtain a greater number of patients with INR out of range[14] than those obtained in the controls of primary care consultations or specialized consultations.

For INR analysis, most studies determine INR time in range or out of range from various determinations. To do this, two methods are used: averaging time in range through several previous controls or using the method described by Rosendaal et al.[18]. In most studies, INR is considered out of range if it is less than 60-65% of the time in range[9,11,12]. In our study, by its characteristics, a single determination of the INR, the one made at the entrance of the patients in the HES was analysed.

Of the total number of patients included in the study, slightly more than half were women, similar to other studies in our environment[9,11,12] in which the percentage of women ranges from 42% to 53%. The mean age of the patients was 76.8 years, also similar to that of other studies. The majority indication for treatment with AVK was non-valvular AF with 86.7% of patients, in 10.6% it was indicated by venous thromboembolic disease and 19.1% were patients with valvular prostheses. Most studies of adequacy of treatment with AVK focus on patients with non-valvular AF. The fact that we collected all the indications of treatment with AVK allows us to verify some data of interest that will be analysed.

As for the different variables associated with poor control of INR, the results are very variable in Spanish studies[9,11,12]. The female sex and age in relation to the younger patients are reported as coincident factors[19-22]. In our study, these and also those with severe dependence most frequently had an out-of-range INR.

A high percentage of patients with a history of stroke were out of range, with frequencies close to statistical significance. Other thromboembolic risk factors included in the $CHADS_2$ or $CHA2DS_2$-Vasc scales (heart failure -IC-, -HTA- and diabetes mellitus -DM-) also occurred more frequently in patients with out-of-range INR. Several studies also relate the parameters that define a greater thromboembolic risk in the $CHADS_2$ or CHA_2DS_2-Vasc scales, with a worse INR control[23,24]. We

believe that some of the factors that are related to the need for a better control of INR, such as factors related to thromboembolic risk scales (patients with a history of hypertension, HF, DM or stroke) or patients with a prosthetic valve, are those that most frequently present an out-of-range INR.

Patients with a prosthetic valve constituted almost a fifth of the sample. Most of these patients were also out of range, although they did not reach statistical significance (p = 0.08). Our patients performed the INR controls in their PCC in most cases, with a percentage similar to those of other Spanish studies, with no significant differences between those who underwent the control in specialized consultation or the PCC. This means that from the perspective of the HES, the place where the INR is controlled is indifferent. A non-significant trend (p = 0.06) was observed in relation to changes in usual pharmacological treatments since the last INR control and an out-of-range INR. This data agrees with the multiple pharmacological interferences presented by AVK and has not been analysed in other Spanish studies[9,11,12].

Finally, those patients who required admission or observation after initial care in HES, more often had a significantly out-of-range INR. This fact probably reflects a greater severity of their pathologies and their decompensation. However, the presence of an out-of-range INR could also have been a factor influencing the observation or entry decision.

The only variable that was independently associated with the presence of an out-of-range INR was the change in usual pharmacological treatments since the last control. This variable is related to the characteristics of AVKs and their interaction with many drugs.

As strengths and limitations of our study, we emphasize that this is a multicentre study that includes 4 hospitals in the city of Barcelona and its province, with an area of influence close to one and a half million inhabitants. Although centres with different characteristics (district hospitals and tertiary referral hospital) were different, the results of the four centres were homogeneous, with no significant differences between them. Patients not treated with AVK for non-valvular AF, but also those with other indications, have been evaluated not only to obtain data of interest, such as those of patients with prosthetic valves. The inclusion of the patients was not consecutive, but a uniform and objective criterion was assured in each center, and between the different centres. This, together with the determination of a single INR value can be interpreted as limitations of the study, but in return it has allowed to approach the situation of common clinical practice. The main limitation of the study is that an opportunity sampling was made to ensure the control of the observers' reliability and, therefore, the study was carried out on the days in which the researcher developed his working day. This type of sampling conditions that the representativeness of the included patients is scarce and restricted, which, in turn, limits the external validity of the study. However, the final sample size, which, although not knowing its representativeness, the results obtained are congruent with those of previous studies published in the literature that collect all the consecutive cases, suggest a lower probability of bias.

Regarding the practical applicability, apart from finding that a high percentage of patients on AVK treatment have out-of-range controls, this study allows us to detect those factors that may predict an out-of-range INR. In these patients, it would be advisable to perform a control. The detection of these patients with out-of-range INR, even in a timely determination, will allow corrective measures and prevention of possible thrombotic and/or haemorrhagic complications to be adopted. As future lines of research, it would be of interest to follow-up out-of-range patients to assess whether they remain at risk or, conversely, the INR can be adjusted. On the other hand, it would be interesting to follow these patients to determine the clinical impact of this situation.

In conclusion, in our study, a high percentage of patients treated with AVK who come to the HES for any pathology unrelated to complications of such treatment have an INR out of therapeutic range. In those patients with changes in the usual treatment since the last control it would be advisable to perform an INR in the HES.

Conflicting interests

The authors declare no conflict of interest reated to this article.

Financing

The authors declare the non-existence of external financing of this article.

Ethical Responsibilities

The study was approved by the Ethics Committees of the four participating centers of the city of Barcelona (CEIC Code 20123008): University Hospital of Mollet, Hospital Universitari, Quirónsalud General University Hospital of Catalonia, Parc Taulí Hospital Universitari and Hospital Clínic.

The study (ALT-AVK-2012-01) was classified by the Spanish Agency of Medicines and Sanitary Products as a Posauthorization Study with other designs than the prospective follow-up "EPA-OD".

Informed consent was obtained from participants.

All authors have confirmed the maintenance of confidentiality and respect for patients' rights in the author's responsibilities document, publication agreement and assignment of rights to EMERGENCIAS.

Article not commissioned by the Editorial Committee and with external peer review

References

1 Sutcliffe FA, MacNicoll AD, Gibson GG. Aspects of anticoagulant action: a review of the pharmacology, metabolism and toxicology of warfarin and congeners. Rev Drug Metab Drug Interact. 1987;5:225-72.

2 Greenblatt DJ, von Moltke LL. Interaction of warfarin with drugs, na-

tural substances, and foods. J Clin Pharmacol. 2005;45:127-32.
3 Witt DM, Delate T, Clark NP, Martell C, Tran T, Crowther M, et al. Twelve-month outcomes and predictors of very stable INR control in prevalent warfarin users. J Thromb Haemost. 2010;8:744-9.
4 Platt AB, Localio AR, Brensinger CM, Cruess DG, Christie JD, Gross R, et al. Risk factors for nonadherence to warfarin: results from the IN-RANGE study. Pharmacoepidemiol Drug Saf. 2008;17:853-60.
5 Heneghan C, Ward A, Perera R, Bankhead C, Fuller A, Stevens R, et al. Self-monitoring of oral anticoagulation: systematic review and meta-analysis of individual patient data. Lancet. 2012;379:322-34.
6 Alonso-Coello P, Zhou Q, Guyatt G. Home-monitoring of oral anticoagulation vs. dabigatran. Thromb Haemost. 2012;108:647-53.
7 Wilson SJ, Wells PS, Kovacs MJ, Lewis GM, Martin J, Burton E, et al. Comparing the quality of oral antico-agulant management by anticoagulation clinics and by family physicians: a randomized controlled trial. CMAJ. 2003;169:293-8.
8 Ryan F, Byrne S, O'Shea S. Randomized controlled trial of supervised patient self-testing of warfarin therapy using an internet-based expert system. J Thromb Haemost. 2009;7:1284-90.
9 Barrios V, Escobar C, Prieto L, Osorio G, Polo J, Lobos JM, et al. Control de la anticoagulación en pacientes con fibrilación auricular no valvular asistidos en atención primaria en España. Estudio PAULA. Rev Esp Cardiol. 2015;78:769-76.
10 Nuevo González JA, Cano Ballesteros JC, Pintor Holguín E, Braun Saro B, Visús Soler E, Sevillano Fernández JA. Exceso de anticoagulación oral: análisis desde un servicio de Urgencias. Rev Clin Esp. 2008;208:66-70.
11 Anguita Sánchez M, Bertomeu V, Cequier A. Calidad de la anticoagulación con antagonistas de la vitamina K en España: prevalencia de mal control y factores Asociados. Rev Esp Cardiol. 2015;68:761-8.
12 Cinza-Sanjurjo S, Rey-Aldana D, Gestal-Pereira E, Calvo-Gómez C. Evaluación del grado de anticoagulación de pacientes con fibrilación auricular en el ámbito de atención primaria de Galicia. Estudio ANFAGAL. Rev Esp Cardiol. 2015;78:753-60.
13 Roldán Rabadán I, Anguita Sánchez M, Marín F, Quesada MA, Camacho Siles J, Peinado R, et al. Tratamiento antiarrítmico actual de la fibrilación auricular no valvular en España. Datos del Registro FANTASIIA. Rev Esp Cardiol. 2016;69:54-60.
14 Piccini JP, Hellkamp AS, Lokhnygina Y, Patel MR, Harrell FE, Singer DE, et al. Relationship between time in therapeutic range and comparative treatment effect of rivaroxaban and warfarin: results from the ROCKET AF trial. J Am Heart Assoc. 2014;3:e000521.
15 Hylek EM, Go AS, Chang Y, Jensvold NG, Henault LE, Selby JV, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med. 2003;349:1019-26.
16 Samsa GP, Matchar DB. Relationship between test frequency and outcomes of anticoagulation; a literature review and commentary with implications for the design of randomized trials of patients self-management. J Thromb Thrombolysis. 2000;9:283-92.
17 Wan Y, Heneghan C, Perera R, Roberts N, Hollowell J, Glasziou P, et al. Anticoagulation control and prediction adverse events in patients with atrial fibrillation. Circ Cardiovasc Qual Outcomes. 2008;1:84-91.
18 Rosendaal FR, Cannegieter SC, Van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost. 1993;69:236-9.
19 Apostolakis S, Sullivan RM, Olshansky B, Lip GY. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin. The SAMe-TT2R2 score. Chest. 2013;144:1555-63.
20 Penning-van Beest FJ, Geleijsen JM, van Meegen E, Vermeer C, Rosendaal FR, Stricker BH. Lifestyle and diet as risk factors for overanticoagulation. J Clin Epidemiol. 2002;55:411-7.
21 Rodríguez F, Hong C, Chang Y, Oertel LB, Singer DE, Green AR, et al. Limited English Proficient Patients and Time Spent in Therapeutic Range in a Warfarin Anticoagulation Clinic. J Am Heart Assoc. 2013;2:e000170.
22 Choi J, Damaraju CV, Mills R, Wildoose P, Fields L, Schein J, et al. Impact of comorbidities on time in therapeutic range in patients with nonvalvular atrial fibrillation. J Am Coll Cardiol. 2012;59(13s1):E1855.
23 Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001;285:2864-70.
24 Lip GY, Nieuwlaat 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. 2010;137:263-72.