Control of Therapeutic Levels of Anticoagulation and Associated Factors: A Prospective Cohort Study

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Abstract

Maintaining therapeutic levels of anticoagulation is essential to avoid health complications in people who take vitamin K antagonists. This study aimed to analyze the influence of people's characteristics and the presence of changes in their lives in the control of therapeutic levels of anticoagulation. A longitudinal multicenter study with a 1-year follow-up of a cohort of 199 people receiving anticoagulant therapy was performed. The effect of biological, clinical, social, lifestyle, and changes in life on the international normalized ratio (INR) was analyzed. During the follow-up, 46.7% of participants presented good INR control. At baseline, a diagnosis of atrial fibrillation ($P=.00$), the lack of comorbidities ($P=.03$), absence of depression ($P=.04$), and not following a pharmacological treatment with hypoglycemia drugs ($P=.01$) were associated with good INR control. During the follow-up, the variable of making changes to the usual diet was associated with poor INR control ($P=.05$). In the binary multiple regression model, factors associated with poor control were taking hypoglycemia drugs ($P=.02$) and the presence of depression ($P=.04$), and only the diagnosis of atrial fibrillation was associated with good control ($P=.03$). People with a diagnosis of atrial fibrillation had good INR control. Having comorbidities, suffering depression, taking hypoglycemia drugs, and making changes to the diet have a negative effect on INR control.

Keywords

anticoagulant therapy, vitamin K antagonists, international normalized ratio control, community care

Dates received: 17 July 2022; revised: 13 September 2022; accepted: 14 September 2022.

Background

Cardiovascular diseases are one of the main causes of death worldwide and 23.6 million such deaths are forecast in 2030.[1] Atrial fibrillation is the most common sustained cardiovascular disease in adults worldwide with a prevalence between 2% and 4%.[2] A 2.3-fold rise is expected owing to extended longevity and intensified searching for undiagnosed atrial fibrillation.[3,4]

Atrial fibrillation is associated with a five-fold increase in the risk of stroke, given that between 20% and 30% of people with ischemic stroke are diagnosed with this disease before, during or after the event. Therefore, atrial fibrillation poses a significant burden to patients, physicians, and healthcare systems globally.[5]

Both preventative and curative treatment of these diseases is through anticoagulation. The decision to anticoagulate patients with atrial fibrillation depends on the stroke risk.[6] In general, oral anticoagulation is indicated in the prevention of cardiac thromboembolism with a CHA2DS2-VASc score ≤2. There are 2 main types of oral anticoagulant therapies: vitamin K antagonists and direct oral anticoagulants. The European Society of Cardiology recommends the use of direct oral anticoagulants instead of vitamin K antagonists when oral coagulation is initiated in patients with atrial

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fibrillation.[5] However, vitamin K antagonists have shown their efficacy in the prevention of thromboembolic events, especially in older people,[7] and are currently the treatment of choice for atrial fibrillation.[8] The use of these antagonists is conditioned by the narrow therapeutic window, which requires monitoring through the international normalized ratio (INR) and frequent dose adjustments.[9]

The general recommendation is to maintain the INR between 2 and 3, although this can vary depending on the reason for the anticoagulant therapy.[9] When INR values are below the recommended range, the risk of stroke is doubled, whereas if INR values are above this range the risk of cerebral hemorrhage increases.[6] Therefore, the maintenance of therapeutic levels of anticoagulation is essential to avoid complications.[10] This treatment is often monitored in primary care settings and professionals from this area are essential both in the diagnosis and in determining the most suitable approach.[11]

People on oral anticoagulant therapy often present out-of-range INR values.[12] Age, comorbidities, poor drug adherence, tobacco and alcohol use, changes in prescribed treatments, dietary changes, and the consumption of herb-based supplements have all been associated with poor INR control.[5,9,12-14]

Knowledge of the characteristics of the population receiving oral anticoagulant treatment and the factors influencing its control provides the basis for establishing care strategies. Although there are studies about treatment with vitamin K antagonists,[15] few are focused on the characteristics we consider in the present study and few published studies report longitudinal controls of this treatment in primary care settings. The present study aimed to analyze the control of therapeutic levels of anticoagulation and to relate this control to people's characteristics and the presence of changes in their lives during the study period.

Methods

Design

A multicenter prospective cohort study with a 1-year follow-up of patients receiving anticoagulant therapy.

Sample

The study population consisted of people treated with vitamin K antagonists and who had INR controls in 1 of the 4 participating primary health care centers located in the Girona Health Region (n=274). Exclusion criteria were having initiated the treatment less than 6 months earlier, being institutionalized or included in the home care program, and being unable to respond to the questionnaires for cognitive reasons.

Instruments

Two ad hoc questionnaires were prepared, one for the first visit and one for successive visits. The first questionnaire consisted of 4 sections: (a) sociodemographic data: age, sex, cohabitation status, educational level, occupation, and primary care center; (b) clinical data: diagnosis, obesity, comorbidities (Charlson Comorbidity Index[16]), cognitive state (Pfeiffer Short Portable Mental Status Questionnaire[17]), depression (The Geriatric Depression Scale[18]), and pharmacological treatment; (c) lifestyle: physical activity and addictions: (tobacco and alcohol) and (d) data related to the treatment with vitamin K antagonists: initiation, preparation of the drug, discomfort with the INR control, discomfort with the vitamin K antagonist therapy, controls with the primary care nurse, and attendance at therapy groups. In the second questionnaire, data was gathered during the INR controls about the following changes and events: pharmacological treatment, changes in diet, intercurrent health problems (such as, eg, viral processes or surgical interventions), and failures to take the dose of the anticoagulation drug. INR control was considered to be good in those patients who had at least 60% of INR controls within the range during the year of follow-up (in accordance with the individually established INR ranges based on the pathology).

In order to increase the validity of the results, both clinical experts (2 experienced case management nurses in cardiac pathology and 1 in hematology) and methodological experts participated in the preparation of the questionnaires. These were administered during the consultation visits with the different primary care nurses who had received specific training for the study.

Before the start of the study, a pilot questionnaire was given to 15 people who were being treated with vitamin K antagonists and who were under INR control at one of the participating primary health care centers, which resulted in minor modifications being made.

Data Collection

Patients were recruited through the primary care nurses. Once included in the study, the baseline visit was set at which the data from the first questionnaire was gathered. Afterward, and over a period of 12 months, a nurse administered the second questionnaire at each of the monthly INR control visits.

Before starting the full study, a pilot test was conducted with 15 patients. No modifications were required as all participants understood all the questions asked.

Ethical Considerations

The study was carried out in accordance with the Declaration of Helsinki and the European Medicine Agency Guidelines for Good Clinical Practice. The study was approved by the

Table 1. Clinical Characteristics of the Sample and Their Relation to INR Control (n 199).

Variable	n (%)	INR control		*P*
		Good control	Bad control	
Diagnoses				
Auricular fibrillation	164 (82.4)	84 (51.2)	80 (48.4)	.00
No auricular fibrillation	35 (17.6)	9 (25.7)	26 (74.3)	
Obesity				
Yes	64 (32.2)	33 (16.6)	31 (15.6)	.34
No	135 (67.8)	60 (30.2)	75 (37.7)	
Comorbidity index				
Comorbidity	27 (13.6)	8 (29.6)	19 (70.4)	.03
No comorbidity	172 (86.4)	85 (49.4)	87 (50.6)	
Cognitive impairment				
Cognitive impairment	36 (18.1)	14 (38.9)	22 (61.6)	.29
No cognitive impairment	163 (81.9)	79 (48.5)	84 (51.5)	
Depression				
Depression	45 (22.6)	15 (33.3)	30 (66.7)	.04
No depression	154 (77.4)	78 (50.6)	76 (49.4)	
Treatment				
Hypoglycemia drugs	48 (24.1)	15 (31.3)	33 (68.8)	.01
Hypolipidemic agents	88 (44.2)	41 (46.6)	47 (53.4)	.97
Antihypertensive drugs	139 (69.8)	64 (46.0)	75 (54.0)	.76
Digestive drugs	80 (40.2)	34 (42.5)	46 (57.5)	.32
Endocrine drugs	14 (7.0)	5 (35.7)	9 (64.3)	.31
Psychoactive drugs	54 (27.1)	28 (51.9)	26 (48.1)	.37
NSAIDs	50 (25.1)	24 (48.0)	26 (52.0)	.83

The categorical variables are described with the absolute frequency and their percentage.
Chi-square test $P < .05$.

territorial research ethics committee. Informed consent for study participation was required.

Data Analysis

The data obtained from the questionnaires was analyzed using IBM SPSS Statistics for Windows (version 21.0; IBM Corp. Released, 2012).

Continuous variables were described as the mean and measures of dispersion (standard deviation, median, and interquartile range). Categorical variables were described in terms of absolute and relative frequencies. The normality of data distribution was analyzed using the Kolmogorov-Smirnov test. Bivariate analyses using the Chi-square test and the independent samples with the Mann-Whitney U test and a binary logistic regression model were used to study the variables associated with INR levels. The level of significance for all analyses was set at $P < .05$.

Results

The final sample included 199 patients (72.9% of the people who were taking anticoagulant therapy during the study period). Of these, 56% (n = 112) were men. The average age of the participants was 75.9 (SD: 9.5), median 78 (IQR 70-83) years. 72.9% lived with other people, 27.1% had intermediate studies, and 43.2% did or had done unqualified work.

About 82.4% of the participants took vitamin K antagonists due to a diagnosis of atrial fibrillation. The mean body mass index of the participants was 28.5 (SD: 4.8) (overweight). 13.6% had a comorbidity index of over 4 points, the mean of the Pfeiffer test was 1.46 (SD: 2.4) points (normal cognitive state), and 18.1% of participants suffered cognitive deterioration. 77.4% of the participants did not present depression. Clinical characteristics of the sample, as well as prescribed treatments, apart from the vitamin K antagonist, are presented in Table 1.

The participants did an average of 4.37 (SD: 4.7) hours of physical exercise per week. With regards to addictions, 62.8% of the participants were nonsmokers and 54.8% consumed alcohol with low risk (Table 2).

The mean time since the initiation of vitamin K antagonist therapy was 76.6 (SD: 80.2) months, and most prepared the drug for themselves (85.9%). 74.4% of the participants did not refer to any discomfort related to the INR control and 75.9% did not refer to any discomfort with regards to the vitamin K antagonist treatment. 85.4% of the participants followed

Table 2. Variables Related to Lifestyle and AVK Treatment and Their Relation to INR Control (n 199).

Variable	n (%)	INR control		P
		Good control	Bad control	
Physical activity				
Moderate	69 (34.7)	36 (52.2)	33 (47.8)	.51
Low	99 (49.7)	44 (44.4)	55 (55.6)	
Sedentary	31 (15.6)	13 (41.9)	18 (58.1)	
Tobacco consumption				
Smoker	25 (12.6)	14 (56.0)	11 (44.0)	.55
Ex-smoker	49 (24.6)	21 (42.9)	28 (57.1)	
Non-smoker	125 (62.8)	58 (46.4)	67 (53.6)	
Alcohol consumption				
Abstinent	89 (44.8)	41 (46.1)	48 (53.9)	.67*
Low risk consumption	109 (54.8)	52 (47.7)	57 (52.3)	
High risk consumption	1 (0.5)	0 (0.0)	1 (100.0)	
Preparation of the drug				
Autonomously	171 (85.9)	81 (47.7)	90 (52.6)	.65
Familiar caregiver	28 (14.1)	12 (42.9)	16 (57.1)	
Discomfort with INR control				
No discomfort	148 (74.4)	68 (45.9)	80 (54.1)	.90
Some discomfort	13 (6.5)	6 (46.2)	7 (53.8)	
Major discomfort	38 (19.1)			
Discomfort with the treatment				
No discomfort	151 (75.9)	70 (46.4)	81 (53.6)	.47
Some discomfort	21 (10.6)	8 (38.1)	13 (61.9)	
Major discomfort	27 (13.5)	15 (55.6)	12 (44.4)	
Checks with primary care nurse				
Yes	169 (85.4)	79 (46.7)	90 (53.3)	.88
No	29 (14.6)	14 (48.3)	15 (51.7)	
Therapy group				
Yes	21 (10.6)	9 (42.9)	12 (57.1)	.70
No	178 (89.4)	84 (47.2)	94 (52.8)	

The categorical variables are described with absolute frequencies and their percentage.
*These results should be considered with caution as the application criteria are not met.
Chi-square test $P < .05$.

controls with their primary care nurse for motives unrelated to INR control and 10.6% had participated in therapy groups of people in treatment with vitamin K antagonists (Table 2).

Results Associated With International Normalized Ratio Control

The results of the study show that 46.7% of patients had good INR control and that there were no significant differences based on age ($P = .59$), sex, whether one lives alone or not, education, occupation, and primary care center.

Good INR control was associated with the following clinical variables: a diagnosis of atrial fibrillation, the lack of comorbidities, absence of depression, and not following a pharmacological treatment with hypoglycemia drugs. Specifically, 51.2% of people with a diagnosis of atrial fibrillation had good INR control ($P < .01$). Poor INR

control was associated with a comorbidity index of more than 4 points (70.4%; $P = .03$). Furthermore, 66.7% of people with a diagnosis of depression had poor INR control ($P = .04$) as did 68.8% of the participants who took hypoglycemia drugs ($P = .01$).

The number of drugs taken by the participants, obesity and cognitive state were not found to be associated with INR control (Table 1).

Physical activity, tobacco, alcohol consumption, the length of treatment with AVK, who prepared the medication, the perception of discomfort associated with the control of the INR or the medication, and following controls with the primary care nurse or participating in peer therapy groups were not found to be associated with control of the INR (Table 2).

In general, people who had intercurrent health problems, especially fever and gastrointestinal problems and those

Table 3. Binary Logistic Regression Model for Variable Associated with INR Control (n 199).

	Dependent variable: INR control				
	B	SE	95% CI	β	*P*
Hypoglycemic drugs	−.811	0.357	0.216-0.912	.44	.02
Diagnosis of auricular fibrillation	.940	0.438	1.085-6.038	2.55	.03
Depression	−.331	0.163	0.522-0.988	.718	.04
Changes in diet	−2.774	1.598	0.003-1.431	.063	.08
R2	.107				
Corrected R2	.143				

Abbreviations: B, coefficient B; β, standardized beta coefficient; 95% CI, confidence interval of 95%; corrected R2, adjusted R-square (adjusted coefficient of determination); R2, R-square, the coefficient of determination; SE, standard error.

that omitted taking some of the doses of AVK showed worse control of the INR, although this was not a significant association. On the other hand, making changes to the diet that is usually consumed was associated with worse control of the INR (1.07 [1.3] vs 1.64 [1.7]; $P < .05$).

The logistic regression model shows that taking hypoglycemia drugs (OR = 0.44, 95% CI 0.216-0.912, $P = .02$) and depression (OR = 0.72, 95% CI 0.522-0.988, $P = .04$) were strongly associated with poor INR control. Only the diagnosis of atrial fibrillation (OR = 2.55, 95% CI 1.085-6.038, $P = .04$) was associated with good control ($P = .03$) (Table 3).

Discussion

This study analyzed the control of therapeutic levels of anticoagulation in relation to people's characteristics and the presence of changes in their lives over a period of 1 year. The results show that just over half of the participants had good control of the INR and that no differences were found in terms of sex and age. Our findings are partially in line with earlier studies. In this respect, people treated with AVK often present out of range INR values,[19,20] especially in women.[5,21]

Most participants took vitamin K antagonists for a diagnosis of atrial fibrillation given the efficacy of this drug in the prevention of thromboembolic events in these patients.[8]

The results of the study associate the presence of comorbidities and depression with a worse control of the INR. Similar results have been found in earlier studies.[5,9,14] Furthermore, Cosanu et al[22] have shown the benefit of changing vitamin K antagonists to direct anticoagulants in people with depression. There is also evidence for this same change being made in people with cognitive deterioration.[23] However, the results of the present study do not find an association between cognitive state and INR control.

In studying the interaction of the vitamin K antagonist with other drugs, it was observed that taking hypoglycemia drugs was associated with worse control of the INR. The effect of some drugs on vitamin K treatments has been

previously reported[5,14] and studies that have analyzed the specific effect of hypoglycemia drugs have suggested opting for a treatment that does not require a periodic adjustment of the dose.[24]

The binary multiple regression model revealed that the presence of a diagnosis of atrial fibrillation is associated with good control of the INR of the participants, on the other hand, a high comorbidity index, depression, and taking hypoglycemia drugs is associated with poor control of the INR.

In terms of lifestyle, despite sedentary participants having more INR controls outside of normal ranges, the study does not show a significant relationship between physical activity and INR control. Previous studies have found that patients that perform physical activity present therapeutic INR ranges that are more correct.[14]

Addiction to tobacco and alcohol have not been associated with INR control in the present study. In contrast, previous studies have found a negative effect of tobacco and alcohol use with INR control.[5,14,15] These differences between our results and those of other studies might be explained by the fact that we had a small sample of people who were smokers and consumed alcohol with lower mean ages and comorbidity indexes.

With regards to the changes that were produced during the phase of follow-up of participants, the results of the study show that people who made changes to their usual diet had worse INR control, as was also found by Violi et al.[25] Other authors have highlighted the effect of various herbs, food, and dietary supplements that are rich in vitamin K on INR control.[26-28] Additionally, many patients on warfarin remain unaware of which foods contain large amounts of vitamin K. Practitioners should advise patients to consume a steady amount of vitamin K in their diet and make sure that they are familiar with which foods contain this vitamin.[29]

We did not find therapeutic adherence, changes in the habitual treatment and intercurrent health problems to be associated with INR control. However, previous studies have associated low therapeutic adherence, making changes
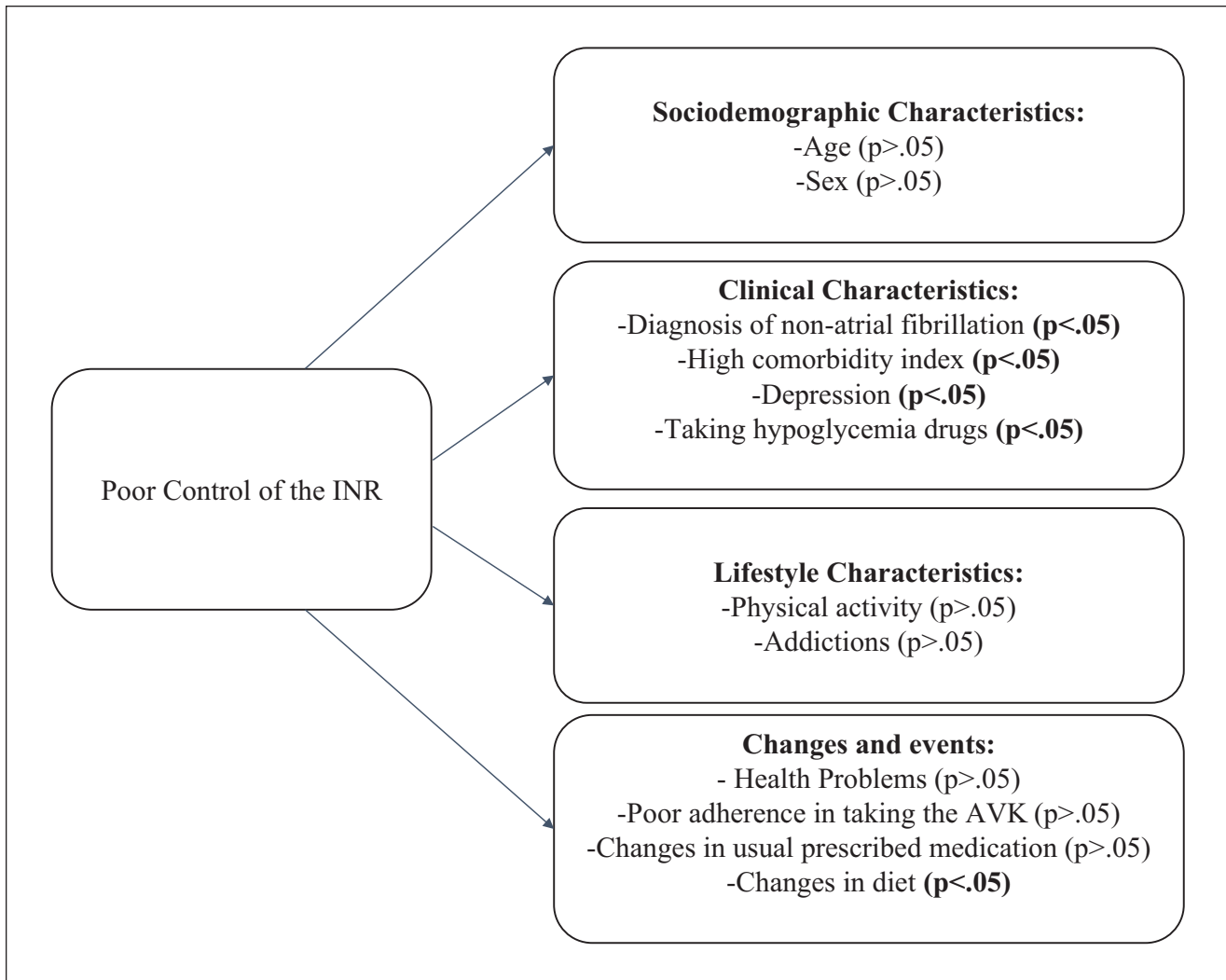
Figure 1. Relationship of INR control with clinical characteristics, social support, lifestyle, and changes and events.

in habitual treatments and the presence of intercurrent problems[5,14] with poor therapeutic control of the INR.

Figure 1 shows the relationship of INR control with clinical characteristics, social support, lifestyle, and changes and events affecting the participants.

This study has some strengths and weaknesses. First, given the variability in INR values, which has been widely described and has many causes, only the best-known influencing factors have been taken into consideration in our study. Second, the variance in the dependent variable explained by the regression model is low. One possible explanation could be that some of the factors studied are present in only a smaller number of people, preventing them from reaching statistical power. Despite these limitations, it should be noted that although there are studies on treatment with vitamin K antagonists, there is no previous research focused on the follow-up of these patients with similar variables in the area of primary care.

Conclusions

Almost half of the people who were controlled for vitamin K antagonist therapy in a primary care setting were found to have good INR control. The diagnosis of non-atrial fibrillation, having comorbidities, depression, and taking hypoglycemia drugs were associated with worse control of the INR. Making changes to one's usual diet was also associated to more INR controls being outside the normal range.

Despite the proven efficacy of vitamin K antagonists in the treatment of cardiovascular diseases, particularly atrial fibrillation, there are still many people who have poor INR control. The present study highlights the characteristics that favor within range INR values for people controlled for vitamin K antagonist therapy in primary care settings. These characteristics can guide us in developing care strategies that optimize the management of this therapy in the most efficient and cost-effective manner.

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References

1. World Health Organization. Cardiovascular diseases. 2017. Accessed June 12, 2021. https://www.who.int/es/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)
2. Benjamin EJ, Muntner P, Alonso A, et al. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. *Circulation*. 2019;139(10):e56-e528.
3. Wilke T, Groth A, Mueller S, et al. Incidence and prevalence of atrial fibrillation: an analysis based on 8.3 million patients. *Europace*. 2013;15(4):486-493.
4. Krijthe B, Kunst A, Benjamin EJ, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J*. 2013;34(35):2746-2751.
5. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur J Cardiothorac Surg*. 2016;50(5):e1-e88.
6. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42(5):373-498.
7. Sommerauer C, Schlender L, Krause M, et al. Correction to: Effectiveness and safety of vitamin K antagonists and new anticoagulants in the prevention of thromboembolism in atrial fibrillation in older adults - a systematic review of reviews and the development of recommendations to reduce inappropriate prescribing. *BMC Geriatr*. 2018;18(1):12. doi: 10.1186/s12877-017-0663-5. Erratum for: BMC Geriatr. 2017;17(Suppl 1):223.
8. Manckoundia P, Rosay C, Menu D, et al. The prescription of vitamin K antagonists in a very old population: a cross-sectional study of 8696 ambulatory subjects aged over 85 years. *Int J Environ Res*. 2020;17(18):6685.
9. Shikdar S, Vashisht R, Bhattacharya PT. International Normalized Ratio (INR). In: StatPearls [Internet]. StatPearls Publishing; 2022.
10. Murphy A, Kirby A, Bradley C. Monitoring of atrial fibrillation in primary care patients prescribed direct oral anticoagulants for stroke prevention. *Ir J Med Sci*. 2020;189(3):961-966.
11. Palareti G, Poli D. The challenges and limitations of widespread direct oral anticoagulant treatment: practical suggestions for their best use. *Expert Rev Cardiovasc Ther*. 2016;14(2):163-176.
12. Al-Momany N, Makahleh ZM, Al-Omari N, Al-Sarayreh H, Momani RO. Analysis of factors that interrupt with INR control in the first anticoagulation clinic monitoring Jordanian patients. *Clin Appl Thromb Hemost*. 2019;25:1076029619870252.
13. Immonen S, Valvanne J, Pitkälä KH. The prevalence of potential alcohol-drug interactions in older adults. *Scand J Prim Health Care*. 2013;31(2):73-78.
14. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2):e44S-e88S.
15. Wehling M, Collins R, Gil VM, et al. Appropriateness of oral anticoagulants for the long-term treatment of atrial fibrillation in older people: results of an evidence-based review and international consensus validation process (OAC-FORTA 2016). *Drugs Aging*. 2017;34(7):499-507.
16. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.
17. Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *J Am Geriatr Soc*. 1975;23(10):433-441.
18. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res*. 1983;17(1):37-49.
19. Barrios V, Escobar C, Lobos JM, Polo J, Vargas D. Uso de los anticoagulantes orales de acción directa en atención primaria: estudio ACTUA. *Semergen*. 2017;43(7):477-485.
20. Urbonas G, Valius L, Šakalytė G, Petniūnas K, Petniūnienė I. The quality of anticoagulation therapy among warfarin-treated patients with atrial fibrillation in a primary health care setting. *Medicina (Kaunas)*. 2019;55(1):15.
21. García-Sempere A, Hurtado I, Bejarano-Quisoboni D, et al. Quality of INR control and switching to non-Vitamin

K oral anticoagulants between women and men with atrial fibrillation treated with Vitamin K Antagonists in Spain. A population-based, real-world study. *PLoS One*. 2019;14(2):e0211681.

22. Cosanu K, Ureyen CM, Yilmaz S. Effect of novel oral anticoagulants on Hospital Anxiety and Depression Scale scores. *Herz*. 2019;44(8):743-749.

23. Besford M, Graham S, Sammon C, et al. Factors associated with non-prescription of oral anticoagulant treatment in non-valvular atrial fibrillation patients with dementia: a CPRD-HES study. *Age Ageing*. 2020;49(4):679-682.

24. Cepeda JM, Arrate V, Facila L, et al. Selecting the best anticoagulant treatment for patients with atrial fibrillation and diabetes or chronic kidney disease: the role of rivaroxaban. *Revista Española de Cardiologia Suplementos*. 2020;20: 39-45.

25. Violi F, Lip GY, Pignatelli P, Pastori D. Interaction between dietary Vitamin K intake and anticoagulation by Vitamin K antagonists: is it really true? A systematic review. *Medicine (Baltimore)*. 2016;95(10):e2895.

26. Di Minno A, Frigerio B, Spadarella G. Old and new oral anticoagulants: foods, herbal, medicines and drug interactions. *Blood Rev*. 2017;31(4):193-203.

27. Tan CSS, Lee SWH. Warfarin and food, herbal or dietary supplement interactions: a systematic review. *Br J Clin Pharmacol*. 2021;87(2):352-374.

28. Ge B, Zhang Z, Zuo Z. Updates on the clinical evidenced herb-warfarin interactions. *Evid Based Complement Alternat Med*. 2014;2014:957362.

29. Rangecroft A, Prabhu SS, Huang CC. Pickles and warfarin interaction: a case-based review. *J Clin Rheumatol*. 2021;40(4):1621-1624.