EPIDEMIOLOGY AND PREVENTION

Changes in the Clinical Profile of Patients Treated with Oral Anticoagulants During the Decade of the Ninety

Eduardo Vázquez Ruiz de Castroviejo, María José Martín Barranco, Antonio Martín Rubio, Antonio Fajardo Pineda, Cristóbal Lozano Cabezas, Manuel Guzmán Herrera, Ada Tarabini Castellani, Carlos Pagola Vilardebó, Eufrasio Martínez Galiano[a] and Antonio Alcalá Muñoz[a]

Unidad de Cardiología y [a]Servicio de Hematología. Hospital Ciudad de Jaén. Jaén.

Introduction. During the last few years the efficacy of oral anticoagulant treatment in the prevention of thromboembolic complications among patients with cardiac diseases has been well established. This has determined an increase in the number of patients undergoing this therapy and a change in the clinical profile of these patients.

Objective. To determine the number and the changes in the clinical characteristics of patients treated with oral anticoagulants during the last decade.

Patients and method. The charts of 5771 hospitalized patients between January 1, 1991 and December 31, 1999, were retrospectively reviewed. We analyzed the number of patients discharged with anticoagulant treatment, the clinical profile and the evolution during the decade.

Results. 761 (13.1%) patients were discharged with anticoagulants. The therapy was prescribed to 7.4% of the patients from 1991-1993 and to 15.1% of the patients from 1998-1999. The mean age of the patients was 60.4 from 1991-1993 and 67.1 from 1998-1999 (p < 0.001). At the beginning of the decade, 90% of the patients had prosthetic valves, suffered from rheumatic heart disease or had had thromboembolic phenomena previously. At the end of the decade, only 49% could be included in these groups.

Conclusions. *a)* The use of oral anticoagulants among our hospitalized patients has been duplicated during the past ten years; *b)* the clinical profile has changed, patients are now older and with different morbidity; *c)* the rheumatic heart disease and the prosthetic valves are no longer the predominant indications, and *d)* the use of therapy as secondary prevention has decreased significantly.

Key words: *Anticoagulants. Population. Atrial fibrillation.*

Cambios en el perfil clínico de los pacientes anticoagulados durante la década de los noventa

Introducción. Durante los últimos años ha quedado bien establecida la eficacia del tratamiento anticoagulante oral en la prevención de complicaciones tromboembólicas en enfermedades cardíacas. Esto ha condicionado un incremento en el número de pacientes sometidos a dicha terapia y un cambio en su perfil clínico.

Objetivo. Determinar el número y los cambios en las características clínicas de los pacientes anticoagulados durante la década de los noventa.

Pacientes y método. Revisamos, de forma retrospectiva, los informes clínicos de alta de 5.771 pacientes hospitalizados entre enero de 1991 y diciembre de 1999. Analizamos el número de pacientes dados de alta con anticoagulantes y los cambios en su perfil clínico durante la década.

Resultados. Un total de 761 (13,1%) pacientes fueron dados de alta con anticoagulantes. En el 7,4% de los enfermos el tratamiento se indicó durante los años 1991-1993 y en el 15,1% durante los años 1998-1999. La edad media fue de 60,4 años durante los años 1991-1993 y de 67,1 años durante 1998-1999 (p < 0,001). Al inicio de la década el 90% de los pacientes eran portadores de prótesis, padecían enfermedad reumática o habían tenido un episodio tromboembólico previo. Al final de la misma, sólo el 49% podía ser incluido en estos grupos.

Conclusiones. *a)* El uso de los anticoagulantes orales entre nuestros pacientes hospitalizados se ha duplicado durante los últimos 10 años; *b)* el perfil clínico ha cambiado y en la actualidad está constituido por pacientes más ancianos y con diferente morbilidad; *c)* la enfermedad reumática y las prótesis valvulares han dejado de ser las indicaciones predominantes, y *d)* el uso de la terapia como prevención secundaria se ha reducido significativamente.

Palabras clave: *Anticoagulantes. Población. Fibrilación auricular.*

INTRODUCTION

Coumarins have been used as oral anticoagulant agents for more than half a century.[1-4] Their proven effectiveness in the prevention of thromboembolism (TE) has firmly associated these drugs with the treat-

ABBREVIATIONS

RCV: rheumatic cardiac valve disease
DM: diabetes mellitus
AF: atrial fibrillation
NRAF: non-rheumatic atrial fibrillation
AHT: arterial hypertension
CHF: congestive heart failure
TE: thromboembolism

ment of certain cardiological diseases. However, anticoagulant treatment carries an evident risk of bleeding, produces numerous drug interactions, and requires costly and complex control that makes patients receiving oral anticoagulants a special group for all healthcare professionals involved in their care. This treatment subjects patients and, occasionally, their families to special restrictions.

Nonetheless, not only have no alternatives been developed for prolonged anticoagulation, but in recent years the number of indications have increased. This, together with the simplification of treatment follow-up, improved transport and communication, and the increased capacity of patients to correctly manage their treatment has lead to a significant increment in the number of patients being treated with oral anticoagulants.[5,6] The population now treated with oral anticoagulants include patients who only a few years ago were thought to present contraindications to anticoagulation for reasons of age, comorbidity, or sociocultural status.

The complexity and cost of treatment means that the rise in the frequency of oral anticoagulant prescriptions entails the dedication of additional resources and modifications in control structures. The changes in the clinical characteristics of patients treated with oral anticoagulants mean that when physicians assess the risk of bleeding, they must invariably consider that this population group has experienced ostensible variations over a short period of time. Special care must be taken in extrapolating study results, even those reported in recent publications.

The aim of this study was to analyze the number of patients treated with oral anticoagulants in our center in the 1990s in order to identify changes in the clinical profile of this patient population.

PATIENTS AND METHOD

We reviewed hospital discharge reports and sometimes the full medical records of 5771 patients admitted to the cardiology department between 1 January 1991 and 31 December 1999. We determined how many patients were discharged with oral anticoagulant treatment with coumarin derivatives, regardless of whether

this treatment had been prescribed before admission or during admission. We analyzed the clinical profile of patients treated with anticoagulants considering the variables of age, sex, presence of atrial fibrillation (AF), previous TE, prosthetic cardiac valves, rheumatic cardiac valve disease (RCV), diabetes mellitus (DM), arterial hypertension (AHT), and congestive heart failure (CHF). The patient was considered to have AF if the arrhythmia was permanent or appeared in prolonged, repeated episodes that categorized the patient in the group of chronic, recurrent, persistent AF and was determinant in establishing the indication for anticoagulant treatment. Previous TE was defined as cerebrovascular accidents, transitory cerebral ischemic episodes, and peripheral embolism. The diagnosis of DM or AHT required that the patient be receiving specific pharmacological treatment for these diseases. The diagnosis of CHF was based on the mention in a hospital discharge report of the presence of this condition.

The evolution of the patients' clinical profiles was evaluated by comparing the first 3 years of the decade (1991-1993) with two-year intervals for the rest of the study period targeted. The absolute number of hospital discharge reports analyzed in each period were 1093 in 1991-1993; 1591 in 1994-1995; 1053 in 1996-1997; and 2034 in 1998-1999. Since admissions rather than patients were studied, all admission of patients who had been hospitalized more than once were counted.

Statistical analysis

Quantitative variables were expressed as means ± 1 standard deviation. Qualitative variables were expressed as percentages and confidence intervals were calculated. The Student t test was used to compare unpaired quantitative variables and the χ^2 test for qualitative variables. A value of P < .05 was considered statistically significant for hypothesis testing.

RESULTS

A total of 761 of the 5771 admissions analyzed (13.1%) were patients discharged with anticoagulant treatment with coumarin drugs. These admissions corresponded to 563 patients and 198 readmissions. The clinical characteristics of the entire group of patients treated with oral anticoagulants are summarized in Table 1. Anticoagulants were prescribed to 7.4% of the patients hospitalized in 1991-1993, and to 15.1% of the patients hospitalized in 1998-1999. The evolution over the decade of the proportion of patients treated with oral anticoagulants and the evolution of the proportion of patients with AF is shown in Figure 1.

The mean age of patients treated with oral anticoagulants was 60.4 ± 9.2 years in 1991-1993 and 67.1 ± 10.5 years in 1998-1999 (P < .001). The percentage of
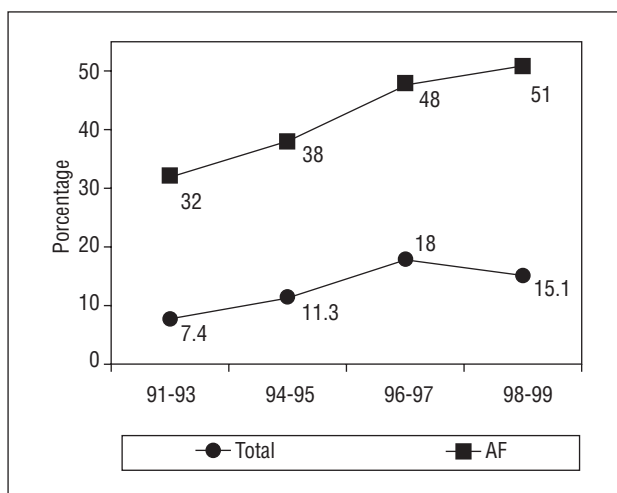
Fig. 1. Evolution of the percentage of patients treated with oral anticoagulants during the 1990s. The percentage of patients treated with oral anticoagulants in relation to all patients hospitalized and in relation to patients with atrial fibrillation is shown. AF indicates atrial fibrillation

patients over 75 years undergoing anticoagulant treatment was 1% at the beginning of the decade and 19% at the end (P < .001). In contrast, the proportion of patients under 60 years decreased from 41% to 20% in the same period (P < .001). The evolution of the age of the patients treated with oral anticoagulants throughout the study period is shown in Table 2.

As can be seen in Table 3, of the factors analyzed presence of DM and CHF, and gender distribution did not differ significantly between the early and late 1990s. AF and AHT were present in a larger percentage of patients in the late 1990s. However, rheumatic heart valve disease, carrying a cardiac valve prosthesis, or previous embolic episodes were circumstances that significantly decreased in frequency between 1991-1993 and 1998-1999 and this change conditioned the clinical profile of the patient population receiving oral anticoagulants.

Upon analyzing the presence of a cardiac valve prosthesis or the diagnosis of RCV, it was apparent that one or the other of them was present in almost 80% of patients treated with oral anticoagulants in 1991-1993, but in only 44% of the patients treated in 1998-1999. If we were to add previous embolic episodes to the analysis, almost all of the patients treated with oral anticoagulants in the early 1990s belonged to one of these three categories, compared with only half of the patients in the late 1990s (Table 4).

DISCUSSION

In our series, the use of anticoagulant treatment in hospitalized patients increased two-fold in the decade of the 1990s, from 7.4% in the early 1990s to 15.1% in the late 1990s. The clinical profile of patients under-

TABLE 1. Clinical characteristics of the patients treated with oral anticoagulants throughout the study period (n = 761)

Age (mean)	64.3 ± 10.5 years (22-88)
> 75 years	80 (10.5)
Men	321 (42.1)
AF	699 (91.8)
Permanent AF	98 (78.5)
Previous TE	50 (6.5)
Prosthetic cardiac valves	167 (21.9)
RCV	416 (54.6)
DM	123 (16.1)
AHT	227 (29.8)
CHF	466 (61.2)

Percentages are shown in parentheses. AF indicates atrial fibrillation; AHT, arterial hypertension; CHF, congestive heart failure; DM, diabetes mellitus; RCV, rheumatic cardiac valve disease; TE, thromboembolism.

TABLE 2. Evolution of the age of patients treated with oral anticoagulants throughout the study period

	1991-1993	1994-1995	1996-1997	1998-1999
Mean age (years)	60	60	66	67
> 75 years (%)	1	2	8	19
< 60 years (%)	40	41	24	20

TABLE 3. Changes in the clinical profile of patients treated with oral anticoagulants at the beginning and end of the 1990s

	1991-1993	1998-1999	P
Male	36 (34.9-37.1)	43 (42.9-43.1)	NS
DM	17 (16.6-17.4)	18 (17.9-18.1)	NS
CHF	53 (52.4-53.6)	63 (62.9-63.1)	NS
AHT	20 (19.6-20.4)	34 (33.9-34.1)	< .01
AF	94 (93.8-94.2)	99 (98.9-99.1)	< .05
Cardiac valve prosthesis	42 (41.4-42.6)	15 (14.9-15.1)	< .001
RCV	74 (73.5-74.5)	2 (41.9-42.1)	.001
Previous TE	21 (20.5-22.5)	8 (7.9-8.1)	< .01

Values are expressed as percentages with the 95% confidence interval in parentheses. AF indicates atrial fibrillation; AHT, arterial hypertension; CHF, congestive heart failure; CI, confidence interval; DM, diabetes mellitus; RCV, rheumatic heart valve disease; TE, thromboembolism.

TABLE 4. Differences in the clinical condition for which anticoagulation was prescribed throughout the study period

	1991-1993 (%)	1994-1995 (%)	1996-1997 (%)	1998-1999 (%)
Patients with PV or diagnosed as RCV	79	67	51	44
Patients with PV, diagnosed as RCV or with PE	90	67	55	49

PE indicates previous embolism; PV, prosthetic valve; RCV, rheumatic cardiac valve disease.

going this type of therapy has changed significantly, now including older patients with different conditions. At present, the mean age of patients treated with anticoagulants is 67 years, and patients over 75 constitute one fifth of the entire patient population treated with anticoagulants. Oral anticoagulant treatment of patients over 75 was exceptional less than 10 years ago. Although it is still debated whether the elderly are at greater risk of bleeding,[7-9] the more advanced age of patients treated with oral anticoagulants is due to the increased use of this therapy in the large group of patients with non-rheumatic atrial fibrillation (NRAF). This disease occurs predominantly in the elderly [10-13] and the benefits of anticoagulation in preventing thromboembolic complications have been firmly established in recent years.[14-19] Half of the patients with AF admitted to our center in 1998-1999 were discharged with oral anticoagulant treatment, although this group also includes patients with rheumatic heart valve disease.

The change in the clinical profile of patients treated with oral anticoagulants reflects not only in a rise in their average age, but also the finding that prosthetic cardiac valves or rheumatic heart valve disease have ceased to be the predominant conditions. In the early 1990s, 4 out of 5 patients treated with oral anticoagulants had one of these two clinical conditions. At the end of the study period, less than half of the patients could be included in this group. The use of anticoagulant treatment as a secondary prevention measure decreased significantly, from 21% in the early 1990s to 8% in the late 1990s. The usefulness of anticoagulants in preventing thromboembolism in the many patients who have NRAF has been widely documented in recent years 14-19 , and has made different types of specialists aware of the problem of primary prevention of stroke.[5,6,20-24] Consequently, the use of oral anticoagulant treatment in this large and growing population group has increased, although probably less than would be considered optimal.[25-28] When we analyzed the presence of cardiac valve disease, previous embolism, or prosthetic cardiac valves together, almost the entire population of patients receiving anticoagulant treatment in the early 1990s belonged to one of these categories, compared with only half of the population at the end of the decade.

The results of the present study have several implications, in our opinion. In first place, the complexity and cost of anticoagulant treatment requires that resource allocation be adapted and anticoagulation strategies planned. These strategies must include dissemination among all healthcare sectors involved in the control of these patients specific information about the care that patients receiving oral anticoagulants require with respect to the important area of drug interactions, as well as precautions in the case of tooth extraction,

minor surgery, etc., should be emphasized. It is evident that a greater level of coordination between specialists (fundamentally hematologists and cardiologists) and primary care physicians is needed.[29,30] The use of capillary blood tests, which are being found to be reliable, can do much to avoid discomfort for patients and enable primary care centers to supervise their care, thus eliminating the need for travel to specialized centers. In selected groups, self-control is feasible.[31-33] This contributes not only to improving the effectiveness of the follow-up of patients receiving oral anticoagulants, but also favors the use of more accurate evidence-based prescription practices. This avoids the need for establishing unnecessary contraindications based on hypothetical bleeding risk in nonclinical situations that actually have more to do with the difficulty of strict follow-up.

Aside from these implications, another aspect of our study results should be discussed. Anticoagulant therapy is, without doubt, the pharmacological treatment that requires the most exhaustive risk-benefit assessment before prescription. The risk is conditioned by the possibility of bleeding complications. However, when determining these complications and making extrapolations from the available information, we find that this information refers to a population that is not the same as the current population of patients receiving anticoagulants.[34,35] In a study made in our center in the mid-1990s and recently published,[36] we established the risk of bleeding in the local population of patients currently undergoing anticoagulant therapy. However, when the population included in this study was compared with the population actually receiving oral anticoagulants, we observed appreciable differences in age and comorbidity. These differences meant that this information was not strictly applicable to determining the risk of hemorrhage in the current patient population, despite the short time period that has elapsed.

Finally, we must note that the situation described has not yet stabilized and will continue to change in coming years. The aging of the population, optimization of the use of anticoagulation in patients with NRAF, ease of treatment management, and even the possibility of including groups of patients with a high risk of thromboembolism have been documented.[37] In this last group of patients anticoagulation has been contraindicated until now.[38] These factors will condition for some time the growing frequency of treatment with oral anticoagulants. The development of alternative drugs to the coumarins is in the preliminary stages and cannot be expected produce any substantial changes in prescription practices soon. Therefore, for the next few years physicians we will still have to deal with a situation that has considerable social and health dimensions.

Study limitations

This information was obtained fundamentally from the database of our cardiology unit. This means that the number of patients analyzed was significantly lower in the early years of analysis because less information was available. However, we believe that the large number of patients analyzed in the period for which less information was available (1093) minimizes the effects of this limitation.

The study was based on admissions rather than on patients. This method, which has been used in other studies that have analyzed similar questions,[5,6] makes it possible to determine the real needs for treatment follow-up. However, this is a limitation for estimating the percentage of the population receiving oral anticoagulant treatment. The fact that we had previously studied this topic 20 helped us to accept this limitation. Finally, all the patients were admitted to the cardiology unit and received anticoagulant treatment for thromboembolic heart disease. Consequently, we have not analyzed patients treated with oral anticoagulants for other reasons or admitted to other departments.

CONCLUSIONS

The use of anticoagulant treatment with coumarin for the prevention of thromboembolism increased twofold in the 1990s among the patients hospitalized in our cardiology unit. The clinical profile of patients receiving oral anticoagulant treatment changed significantly in this decade and now corresponds to that of older patients being treated for different diseases. Rheumatic heart disease, prosthetic cardiac valves, and secondary prevention are no longer the predominant indications.

REFERENCES

1. Campbell HA, Link KP. Studies on the hemorrahagic sweet clover diesease, IV: the isolation and crystallization of the hemorrhagic agent. J Biol Chem 1941; 138: 21-33.
2. Stahmann MA, Heubner CF, Link KP. Studies on the hemorrhagic sweet clover disease, V: identification and synthesis of the hemorrhagic agent. J Biol Chem 1941; 138: 513-527.
3. Butt HR, Allen EV, Bollman JL. A preparation from spoiled sweet clover wich prolongs coagulation and prothombin time of the blood: preliminary reports of experimental and clinical studies. Mayo Clin Proc 1941; 16: 388-395.
4. Link KP. The discovery of dicumarol and its sequels. Circulation 1959; 19: 97-107.
5. Stafford RS, Singer DE. National patterns of warfarin use in atrial fibrillation. Arch Intern Med 1996; 156: 2537-2541.
6. Stafford RS, Singer DE. Recent national patterns of wafarin use in atrial fibrillation. Circulation 1998; 97: 1231-1233.
7. Stroke Prevention in Atrial Fibrillation investigators. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation. Stroke Prevention in Atrial Fibrillation II study. Lancet 1994; 343: 687-691.
8. Fihn SD, Callahan CM, Martin DC, McDonell MB, Henikoff JG, White RH et al, for The National Consortium of Anticoagulation. The risk for and severity of bleeding complications in elderly patients treated with warfarin. Ann Inten Med 1996; 124: 970-979.
9. Palareti G, Hirsh J, Legnani C, Manotti C, D'Angelo A, Pengo V et al. Oral anticoagulation treatment in the elderly: a nested, prospective, case-control study. Arch Intern Med 2000; 160: 470-478.
10. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk fator for stroke: the Framingham study. Stroke 1991; 22: 983-988.
11. Lake RR, Cullen KJ, de Klerk NH, McCall MG, Rosman DL. Atrial fibrillation in an elderly population. Aust N Z J Med 1989; 19: 321-326.
12. Philips SJ, Whisnant J, O'Fallon WM, Frye RL. Prevalence of cardiovascular disease and diabetes in residents of Rochester, Minnesota. Mayo Clin Proc 1990; 65: 344-359.
13. Furberg CD, Psaty BM, Manolio TA, Gardin JM, Smith VE, Rautaharju RM. Prevalence of atrial fibrillation in elderly subjects: the Cardiovascular Health Study. Am J Cardiol 1994; 74: 238-241.
14. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomized trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. Lancet 1989; 1: 175-179.
15. The SPAF Investigators. The Stroke Prevention in Atrial Fibrillation Study Group Investigators: final results. Circulation 1991; 84: 527-539.
16. Connolly SJ, Laucpacis A, Gent M, Toberts RS, Cairns JA, Joyner C, for the CAFA study coninvestigators. Canadian Atrial Fibrillation Anticoagulation (CAFA) study. J Am Coll Cardiol 1991; 18: 349-355.
17. Ezekowitz MD, Bridgers SL, James KE, Carliner NH, Colling CL, Gornik CC et al, for the Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. N Eng J Med 1992; 327: 1406-1412.
18. The Boston Area Anticoagulation Trial for Atrial Fibrillation investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibillation. N Engl J Med 1990; 323: 1505-1511.
19. Stroke Prevention in Atrial Fibrillation investigators. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: stroke prevention in atrial fibrillation III randomised clinical trial. Lancet 1996; 348: 633-638.
20. Vázquez E, Martín Rubio A, Pousibet H, Lozano C, Guzmán M, Tarabini A et al. Utilización del tratamiento anticoagulante en los pacientes con fibrilación auricular no reumática. Rev Esp Cardiol 2000; 53: 200-204.
21. Sánchez JF, García L, Chiquero M, Lozano G, Pérez S, Alonso T et al. Tratamiento antitrombótico en la fibrilación auricular no reumática. ¿Cumplimos las recomendaciones de los ensayos clínicos? An Med Interna 1999; 16: 569-573.
22. Falco Ferrer V, Len Abad O, Iglesias Saez D, Pérez Vega C, Reina D, Rosello J et al. Análisis de los factores asociados con la indicación de tratamiento anticoagulante en la fibrilación auricular crónica. Estudio prospectivo de 170 pacientes ingresados en un servicio de medicina interna. Rev Clin Esp 2000; 200: 203-207.
23. Peditier R, Pérez R, Guillén F. Fibrilación auricular y anticoagulación. Experiencia del servicio de Geriatría del HU de Getafe. Rev Esp Geriatr Gerontol 1997; 32: 319-323.
24. Brotons C, Moral I, Anton JJ, Cobos M, Cucurull E, Gállego C et al. Tratamiento preventivo de la fibrilación auricular no reumática: de la eficacia de los ensayos clínicos a la efectividad en la práctica clínica. Aten Primaria 1997; 20: 367-371.
25. Vázquez E. Tratamiento anticoagulante: nuevos aspectos de una antigua terapia. Rev Clin Esp 1999; 199: 89-94.

26. Flaker GC, McGowan DJ, Boechler M, Fortune G, Gage B. Underutilization of antithrombotic therapy in elderly rural patients with atrial fibrillation. Am Heart J 1999; 137: 307-312.

27. Bungard TJ, Ghali WA, Teo KK, McAlister FA, Tsuyuki RT. Why do patients with atrial fibrillation not receive warfarin? Arch Intern Med 2000; 160: 41-46.

28. Connolly SJ. Anticoagulation for patients with atrial fibrillation and risk factors for stroke. Warfarin reduces the risk for two thirds, but doctors still aren't prescribing it enough. BMJ 2000; 320: 1219-1220.

29. Alonso Roca R, Barroso Muñoz C, Álvarez Solanes I, Alcaraz Bethancourt A, Puche López N, Gordillo Lopez FJ. Situación actual del control de la anticoagulación oral en atención primaria. Aten Primaria 1999; 24: 127-133.

30. Fitzmaurice DA, Hobbs FD, Murria ET, Holder RL, Allan TF, Rose PE. Oral anticoagulation management in primary care with the use of computerized decision support and near-patient testing: a randomized, controlled trial. Arch Intern Med 2000; 160: 2343-2348.

31. Taborsky U, Muller-Berghaus G. State-of-the-art patient self-management for control of oral anticoagulation. Semin Thromb Hemost 1999; 25: 43-47.

32. Watzke HH, Forberg E, Svolba G, Jimenez-Boj E, Krinninger B. A prospective controlled trial comparing weekly self-testing and self-dosing with the standard management of patients on stable oral anticoagulation. Thromb Haemost 2000; 83: 661-665.

33. Cromheecke ME, Levi M, Colly LP, de Mol BJ, Prins MH, Hutten BA et al. Oral anticoagulation self-management and management by a specialist anticoagulation clinic: a randomized cross-over comparison. Lancet 2000; 356: 97-102.

34. Landefeld CS, Beyth RJ. Anticoagulant-related bleeding: clinical epidemiology, prediction, and prevention. Am J Med 1993; 95: 315-328.

35. Reverter JC, Tàssies D, Maragall S, Monteagudo J, Escolar G, Ordinas A. Accidentes hemorrágicos durante el tratamiento ambulatorio prolongado con acenocumarol. Med Clin (Barc) 1995; 105: 127-130.

36. Vázquez E, Trujillo M, Lozano C, Avellaneda C, Guzmán M, Martínez E et al. Complicaciones hemorrágicas del tratamiento anticoagulante. Análisis de factores predictores de riesgo. Sangre 1999; 44: 216-221.

37. Vázquez E, Sánchez-Perales C, Borrego F, García Cortés MJ, Lozano C, Guzmán M et al. Influence of atrial fibrillation on the morbido-mortality of patients on hemodialysis. Am Heart J 2000; 140: 886-890.

38. Heras M, Fernández-Ortiz A, Gómez-Guindal JA, Iriarte JA, Lidón RM, Pérez-Gómez F et al. Guías de actuación clínica de la Sociedad Española de Cardiología. Recomendaciones para el uso del tratamiento antitrombótico en cardiología. Rev Esp Cardiol 1999; 52: 801-820.