Morbidity and Mortality in Patients Treated With Oral Anticoagulants

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Introduction and objectives. The number of patients receiving oral anticoagulant therapy has increased markedly in recent years, with the consequence that monitoring must be decentralized. The aim of this study was to provide reference values for the quality of care in patients receiving oral anticoagulants at large specialized Spanish centers for use in future comparative analyses.

Methods. The records of 20 347 outpatients who were receiving oral anticoagulants between January and December 2003 at 4 large Spanish centers were assessed. Databases at the four hospitals were searched for severe adverse events.

Results. In total, 211 987 regular check-ups were carried out, 72.7% of which gave international normalized ratios (INRs) within the range 2–4. Overall, 2369 hemorrhagic events were observed, 190 (8%) of which were severe, with 20 deaths (0.1 per 100 patient–years). In addition, there were 299 thromboembolic events, with 11 deaths (0.05 per 100 patient–years). The frequency of these events was greater in patients with a cardiac prosthesis, who required more intense anticoagulation. The incidence of death with different diagnoses was also greater in anticoagulated patients with a cardiac prosthesis, and the highest probability of death (1 in 3) was associated with episodes of cerebral hemorrhage. The incidence of hemorrhage increased as the INR increased. In contrast, thrombotic events occurred principally when the INR was below 2, and were not observed with INRs over 6.

Conclusions. The incidence of adverse events in patients receiving oral anticoagulant therapy at large Spanish centers was similar to that observed in other European countries.

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Morbilidad y mortalidad en pacientes con tratamiento anticoagulante oral

Introducción y objetivos. El número de pacientes en tratamiento anticoagulante oral (TAO) ha crecido notablemente en los últimos años y ha demandado un proceso de descentralización de los controles. El objetivo de este estudio es tener una referencia de los índices de calidad de la población en TAO seguida en grandes unidades especializadas de España que permita un análisis comparativo futuro.

Métodos. Se valoraron desde enero a diciembre de 2003 las fichas de los 20.347 pacientes en TAO controlados en 4 grandes unidades del país. Se buscó efectos adversos severos en los ficheros informatizados de los 4 hospitales.

Resultados. Se realizaron 211.987 controles, y el 72,7% está dentro de un rango de 2-4. Se detectaron en total 2.369 eventos hemorrágicos, 190 (8%) graves, con 20 fallecimientos (0,1/100 pacientes/año). Hubo 299 episodios tromboembólicos con 11 fallecimientos (0,05/100 pacientes/año). La frecuencia de estos eventos fue mayor en aquellos enfermos con prótesis cardiacas, que precisaban una mayor intensidad de anticoagulación. La incidencia de fallecimientos por diagnósticos fue también mayor en pacientes anticoagulados por prótesis cardiacas y la mayor probabilidad de muerte (1 de cada 3 pacientes) se asoció a episodios de hemorragia cerebral. La incidencia de hemorragia se incrementó en función de la prolongación del INR, mientras que los eventos trombóticos aparecieron especialmente con INR < 2, y no se detectaron con INR > 6.

Conclusiones. La incidencia de efectos adversos que afectan a los pacientes en TAO controlados en grandes unidades del país es similar a las reconocidas en otros países occidentales.

Palabras clave: *Anticoagulantes. Complicaciones. Embolia. Fibrilación auricular. Hemorragia. Infarto de miocardio. Prótesis valvular.*

ABBREVIATIONS

AF: atrial fibrillation
AMI: acute myocardial infarction
CNS: central nervous system
CVA: cerebrovascular accident
DVT: deep vein thrombosis
IHD: ischemic heart disease
INR: international normalized ratio
OAT: oral anticoagulant treatment
PE: pulmonary embolism
RR: relative risk
TED: thromboembolic disease
TIA: transient ischemic attack
UGB: upper gastrointestinal bleeding

INTRODUCTION

The recent increase in the number of indications for prophylactic antithrombotic therapy with vitamin K antagonists and the increased longevity of the population have led to a marked increase in the number of patients who could benefit from this type of treatment.[1,2] Vitamin K antagonists are effective, but have a narrow therapeutic range and an activity that is easily affected by factors such as diet and the use of other drugs.[3] The main consequences of imbalances in activity are a failure to prevent thrombosis (lack of efficacy) or the occurrence of bleeding complications as a result of excessive activity. The minimization of these risks requires periodic follow-up to adjust the dose of the drug to within a safe therapeutic range for anticoagulation based on an analytic test known as the international normalized ratio (INR).[4] There is a strong relationship between the time that patients are in the target range and the appearance of adverse events,[3,5] and as a result, monitoring of treatment with vitamin K antagonists should meet certain internationally recognized quality criteria.[3,6] The main criteria are the number of patients in the therapeutic range, the incidence of severe bleeding and thrombotic events, and mortality.[3] The increased number of appointments required to monitor treatment with vitamin K antagonists, patient difficulties in attending those appointments, and the appearance on the market of small devices to allow assessment of INR have led health authorities to initiate programs of decentralization that will affect a large number of patients. There is no data in the literature regarding the safety of applying this new system of follow-up compared with that carried out in specialist units, but it seems clear that comparative studies should be undertaken.[3] The aim of this study was to identify reference values for quality in patients receiving anticoagulant therapy with vitamin K antagonists in large specialist units in Spain for use in future comparative studies in order to optimize the quality of care received by these patients.

METHODS

The records were analyzed for patients receiving oral anticoagulant therapy (OAT) with vitamin K antagonists between January 1 and December 31, 2003, in 4 large Spanish anticoagulation units serving 1 541 914 inhabitants (Hospital Ramón y Cajal in Madrid, Hospital Clinic i Provincial, and Hospital de Santa Creu i de Sant Pau in Barcelona, and Hospital La Fe in Valencia).

Demographic data, diagnosis, INR, patients within the target range, and mild bleeding complications (defined as those that did not require medical attention) were extracted from the computer program for monitoring of OAT check-ups (HYAT-C) provided by IZASA (Barcelona, Spain). Moderate bleeding complications (defined as those requiring medical treatment), severe bleeding complications (defined as those requiring hospital admission, transfusion of blood products, reduction of hemoglobin levels by more than 2 g/dL, or a requirement for specialist care, including surgery), and thromboembolic events were obtained from the electronic records of each of the hospitals. In Hospital Ramón y Cajal, efforts were made to establish telephone contact with patients who had been lost to follow-up (no recorded visits for more than 3 months).

The vitamin K antagonist that was used was acenocoumarol (Sintrom®, Novartis). The INR was assessed in capillary blood at Hospital Ramon y Cajal (using the Thrombotest method; Axis-Shield, Oslo, Norway) and in venous blood in the other hospitals: STA (Roche Diagnostic, Barcelona, Spain) at Hospital Clinic i Provincial in Barcelona and Thrombotest (Axis-Shield) at Hospital de Santa Creu i de Sant Pau in Barcelona, and Hospital La Fe in Valencia.

Statistical Analysis

Analysis of the significance of events according to the INR interval was done with linear-by-linear association and the Mantel-Haenszel χ^2 test and by logistic regression with events in the INR range of 2 to 3 as the dependent variable.

RESULTS

A total of 20 347 records were identified, indicating that 13.19 patients per 1000 inhabitants received OAT; atrial fibrillation (AF) was the main indication (47.1%) for administration of OAT (Table 1). A total of 211 987 routine follow-up appointments were carried out, with a mean of 10.4 per patient per year; 72.7% were in the INR range of 2 to 4, 16.9% were below 2, and 10.3% above 4. The mean weekly dose of acenocoumarol ranged from 13.2 to 15.5 mg. Of the 7582 patients registered at Hospital Ramón y Cajal, 54% were women and the mean (SD) age was 64.9 (14.6) years (range, 6-101 years). Nine patients could not be contacted.

TABLE 1. **Study Sample According to Hospital Area**[a]

	Hospital[b]						
	A	B	C	D	Total	%	No. per 1000 Inhabitants
Population served	539 472	400 000	285 000	317 442	1 541 914		
Patients receiving OAT	7582	5136	3471	4158	20 347		
OAT per 1000 inhabitants	14.05	10.27	12.18	13.1	13.19		13.19
Cardiac valve prosthesis	1052	1230	533	974	3789	18.6	2.3
Valve disease	565	608	293	384	1850	9.1	1.12
Myocardial disease	186	60	157	244	647	3.2	0.39
Atrial fibrillation	4151	2022	1723	1691	9587	47.1	5.83
Cerebrovascular accident	347	57	202	126	732	3.6	0.44
Thromboembolic disease	781	483	362	319	1945	9.6	1.26
AMI/IHD/bypass	293	65	106	—	464	2.3	0.28
Other	357	259	95	420	1131	6.5	0.68
Total	7582	5136	3471	4158	20 347		
Number of appointments	64 579	58 737	54 509	34 162	211 987		
Sintrom, mg/wk	15.4	15.5	13.2	13.5			
Appointments/patient/y	8.52	11.43	15.70	8.21	10.42		

[a]AMI indicates acute myocardial infarction; IHD, ischemic heart disease; OAT, oral anticoagulant therapy.
[b]A indicates Hospital Ramón y Cajal; B, Hospital Clínic i Provincial; C, Hospital de la Santa Creu i de Pau; D, Hospital La Fe.

TABLE 2. **Site of Bleeding Complications**[a]

Site	Mild or Moderate	Severe	Total	%
Epistaxis	603	7	610	25.75
Bleeding gums	340	—	340	14.35
Cutaneous/muscular	618	14	632	26.67
Ocular	92	2	94	3.96
Hemoptysis	53	7	60	2.53
Hemarthrosis	18	1	19	0.8
Gynecologic	71	13	84	3.54
Hematuria	238	12	250	10.55
Proctorrhagia	101	13	114	4.81
UGB	5	38	43	1.81
Melena	27	36	63	2.65
Internal bleeding		4	4	0.16
Cerebral	2	43	45	1.9
Other	11		11	0.46
Total	2179 (91.98%)	190 (8.02%)	2369	
Deaths	—	20	20	0.84

[a]UGB indicates upper gastrointestinal bleeding.

A total of 2369 bleeding events were detected, of which 92% were mild or moderate and 8% (190 episodes) severe, with 20 deaths (0.1 per 100 patients per year). The majority of the bleeding episodes were cutaneous or mucosal, but in 1.9% of cases they were cerebral (Table 2). There were 299 thromboembolic events (Table 3), with 11 deaths (0.05 per 100 patients per year). The frequency of those events was higher in patients with cardiac valve prostheses, who required more intensive anticoagulation therapy, than in patients with other indications for OAT (Table 4). Thus, the incidence of deaths according to diagnosis was also higher in patients receiving anticoagulant therapy for cardiac valve prostheses and the greatest probability of death (1 in 3 patients) was associated with episodes of cerebral hemorrhage (Table 5). The incidence of bleeding increased with increasing INR, with a relative risk (RR) compared to an INR of 2 to 3 that ranged from 1.7 for an INR of 3 to 4 to 40.4 for an INR greater than 8 (Table 6). Thrombotic events had an RR of 3.4 in patients with an INR of 1 to 2, 0.59 in patients with an INR of 3 to 4, and no further reduction was found for higher values of INR (Table 6). The total number of severe adverse reactions affecting the central nervous system followed a similar pattern (Table 6). In total, 310 patients required hospital admission, 181 for bleeding episodes, especially in the digestive tract, and 129 for thromboembolic events (Table 7).

DISCUSSION

In the study sample, 1.3% of the population received anticoagulant treatment, a percentage that is similar to

TABLE 3. **Thromboembolic Events**[a]

	Total	%
Central nervous system	208	
TIA	107	29.3
CVA	101	27.7
Deaths	9	
Cardiac	30	
AMI/IHD	25	6.8
Valve occlusion	4	1.1
Deaths	1	
Other sites	61	
Peripheral emboli	20	5.5
Peripheral thrombosis	26	7.1
Rethrombosis	15	4.1
Deaths	1	
Total	299	
Deaths	11	

[a]AMI indicates acute myocardial infarction; CVA, cerebrovascular accident; IHD, ischemic heart disease; TIA, transient ischemic attack.

data reported for Spain,[1,2,7,8] with a marked increase in recent years due to longevity and the use of this treatment in many patients with AF,[8,9] which represented the most common diagnosis in our study, as has also been found in other studies.[7-9]

Both the requirement for acenocoumarol and the number of follow-up appointments per patient per year observed in this study were consistent with previously published data.[8,9] Furthermore, the proportion of patients in the therapeutic range was similar to that found in other studies.[8,9]

It is important, from a health care perspective, to know whether the number of patients receiving anticoagulant therapy is in proportion to the demand associated with their respective conditions. The patients who would be candidates for this treatment can be deduced from the published figures for each disease. The most common condition was AF. The prevalence of this entity in the general population is 0.8%,[10] meaning that there could be 4000 patients aged over 65 years with this diagnosis per million inhabitants.[11-13] More detailed studies involving stratification according to age have found that the prevalence of AF is 5% between 60 and 70 years of age, 14% between 70 and 90 years, and greater than 22% in patients aged over 90 years.[14-16] Although the indication for treatment is gradually being applied, in some studies only 60% of patients with AF who did not have contraindications for OAT (40%) received this treatment,[17-19] meaning that is was only used in a third of these patients.[20] As a consequence, considering various studies addressing the origin of stroke, 40% previously had AF and were not receiving anticoagulant therapy.[21-23] In addition, studies have shown that 15% of patients with AF had signs of asymptomatic focal cerebral damage[24] and 93% had silent cerebral infarctions.[25] It should be taken into consideration that the current population of Spain displays a high rate of longevity (18% aged over 65 years), and would therefore be prone to this heart condition. Considering those age groups in the study population (taking the population distribution of the records from Hospital Ramón y Cajal as a reference), the distribution would be as follows: 210 000 patients aged 60-70 years, 135 000 aged 71-80, and 65 000 aged above 81 years. In other words, 40 000 patients in the study group would be expected to have a diagnosis of AF. Of those, 9600 currently receive OAT, but since this treatment indication has been introduced recently and the increases in recent years have been more than 20% per year, it is to be expected that in the immediate future the rate will reach 50% of patients with AF (equivalent to 20 000 patients). For other heart disease (valve disease, myocardial disease, or ischemic heart disease) the rate is much lower.

Cardiac valve prostheses are the second most common reason for OAT in patients with heart disease and corresponded to 3789 patients in this study (0.23% of the study group); this number should correspond to the total number of patients with valve prostheses given that OAT is obligatory in those patients. This rate does not necessarily reflect the mean incidence in Spain, as the patients came from referral hospitals and this may have led to an increased number of patients with this diagnosis.

Venous thromboembolic disease, which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), was a major indication for treatment with vitamin K antagonists in this study. DVT has a prevalence of 50 cases per 100 000 inhabitants and a mortality of 5%,[26] and in 25% of patients there are post-thrombotic sequelae.[27] The prevalence of PE, assuming that only half of all possible cases are diagnosed, could reach 50

TABLE 4. **Cerebral Complications and Underlying Disease**

Diagnosis	Patients	Cerebral Hemorrhage	Cerebral Embolism
Prosthesis	3789	16 (0.42%)	35 (0.92%)
Atrial fibrillation	9587	17 (0.17%)	38 (0.39%)
Myocardial disease	647	0	4 (0.61%)
Valve disease	1850	3 (0.16%)	11 (0.59%)
Ischemic heart disease	464	1 (0.21%)	2 (0.43%)
Other	4010	8 (0.2%)	11 (0.27%)
Total	20 347	45 (0.22%)	101 (0.49%)

TABLE 5. **Mortality According to Underlying Disease and Cause**[a]

	Patients, No.	Deaths, No.	Rate
By diagnosis			
Prosthesis	3789	12	1/316
Atrial fibrillation	9587	10	1/959
Other	6971	9	1/774
Subtotal	20 347	31	1/656
By cause			
Thromboembolism			
CVA	101	9	1/11
Other TED	198	2	1/11
Subtotal	299	11	1/27
Bleeding			
Cerebral	45	14	1/3
Other	136	6	1/22
Subtotal	181	20	1/9

By Site	Cerebral	Other	Total
Thromboembolism			
Prosthesis	5	1	6
Atrial fibrillation	3	0	3
Other	1	1	2
Subtotal	9	2	11
Bleeding			
Prosthesis	6	0	6
Atrial fibrillation	3	4	7
Other	5	2	7
Subtotal	14	6	20
Total	23	8	31

[a]CVA indicates cerebrovascular accident; TED, thromboembolic disease.

TABLE 6. **Relationship Between Events and INR**[a]

INR Range	<2	2-3	3-4	4-5	5-6	6-7	7-8	>8
Thromboembolism, %[b]	0.34	0.10	0.06	0.05	0.05			
Relative risk[b]	3.4		0.6	0.47	0.44			
P	<.0001		.012	NS	NS			
CNS episodes	48	29	13	3	1			
Bleeding, %[c]	0.39	0.32	0.54	1.04	3.29	6.30	6.51	11.43
Relative risk[b]			1.7	3.3	10.5	20.9	21.4	40.4
P			<.001	<.001	<.001	<.001	<.001	<.001
CNS episodes	5	16	7	7		1	2	1

[a]CNS indicates central nervous system; INR, international normalized ratio.
[b]In relation to the INR interval 2-3.
[c]Expressed as a percentage the number of events in relation to the total number of appointments within this interval.

per 100 000 inhabitants and could be the cause of death in 10 patients per 100 000 inhabitants.[28] Systematic use of prophylactic measures in diseases and procedures at risk for thrombosis have led to a remarkable reduction in DVT and PE, mainly in relation to surgery.[29,30] However, there is still a large number of cases reflected in hospital admission, representing a mean of 600 new cases per million inhabitants per year. In our study population, 1900 patients were receiving anticoagulant therapy (acute and chronic treatment), representing a prevalence for this treatment of 1150 patients per million inhabitants. Other diseases would justify the treatment of another 2500 patients per million inhabitants per year.[31]

Bleeding episodes were the most frequent complications. There was a marked variability between participating hospitals in terms of mild episodes; this is probably accounted for by differences in the criteria applied during data collection. However, in relation to severe bleeding, the rates were homogeneous and represented an acceptable incidence (0.009 per patient per year) similar to that described by other authors.[3,8] Digestive tract bleeding was the main cause of hospital

TABLE 7. **Total Number of Admissions According to Event**

	Total	Deaths
Bleeding		
Cerebral	47	14
Gastric	34	
Melena	27	
Proctorrhagia	13	
Hematuria	9	2
Gynecologic	9	
Hematemesis	11	
Hematomas	10	
Epistaxis	6	1
Hemoperitoneum	4	1
Intracavitary	2	
Hemoptysis	4	1
Hemarthrosis	2	
Other	3	1
Subtotal	181	20
Emboli		
Cerebrovascular accident/transient ischemic attack	108	9
Thromboembolic disease	9	1
Acute myocardial infarction/ischemic heart disease	10	
Valve thrombosis	2	1
Subtotal	129	11
Total	310	31

admission and cerebral hemorrhage was associated with the highest mortality. It is noteworthy that 638 cases of cerebral hemorrhage were identified in the general population treated in the hospitals involved in the study (0.04% of the reference population), of whom only 45 (7%) were receiving OAT and monitored by the participating hospitals. In addition, there were another 30 episodes of cerebral bleeding in patients receiving OAT who came from other centers. In other words, only 60% of the cerebral hemorrhages occurring in patients receiving anticoagulant therapy occurred while monitored by specialists, who would logically be expected to treat the majority of patients receiving anticoagulant therapy in the corresponding health care area, and OAT was the cause in only 4.3% of the cerebral hemorrhages that occurred in patients admitted to those hospitals.

In this same group, 2483 (0.15% of the reference population) episodes of cerebral embolism (including cerebrovascular accident [CVA] and transient ischemic attack) were recorded, of which only 8.4% (208 cases) occurred in patients receiving OAT (0.005 episodes per patient per year). The indication for OAT most often associated with cerebral embolism was cardiac valve prosthesis in 101 cases (0.03 per patient per year), while only 49 episodes (0.005 per patient per year) occurred in patients with AF. This contrasts with the 464 episodes of cerebral embolism (0.046 per patient per year) registered in patients with AF who were not receiving OAT, representing a 9-fold higher risk. These data indicate that 70% of cerebral emboli diagnosed occur in patients with AF who are not receiving anticoagulant therapy.

Twenty patients died as a result of bleeding complications (1 per 1017 patients treated). Eleven patients died during thromboembolic complications (1 per 1849 patients treated). The episodes associated with the highest mortality were cerebral hemorrhage (1 in 3 patients) and cerebral embolism (1 in 12 patients), while bleeding complications in the digestive tract were associated with a lower mortality (1 in 91 patients).

To compare the incidence of death associated with these diseases in patients not receiving OAT, the results obtained in Hospital Ramón y Cajal during the study period were assessed. Thus, of 141 cerebral hemorrhages, there were 33 in-hospital deaths (1 in 4 patients) and from a total of 164 cases of CVA, 18 in-hospital deaths were recorded (1 in 9 patients). These data are similar to those in patients receiving anticoagulant therapy, indicating that OAT is not associated with worse prognosis in these conditions.

There is a clear relationship between the thromboembolic events that occur in these patients and an INR for anticoagulant therapy of less then 2. However, the relationship between the degree of anticoagulation and cerebral hemorrhage is weaker.

CONCLUSIONS

The results of this study show that the main indicators of quality, such as the proportion of patients within the target range for anticoagulation and frequency of adverse events, registered in a large population of patients receiving OAT monitored in 4 specialist units are very acceptable and similar to those described for specialist units in other European countries. These values should serve as reference values with which to assess the quality of OAT monitoring in other decentralized settings that are predicted to gradually substitute the monitoring system currently used in Spain.

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