

BMJ Open Adverse drug reactions to anticoagulants in Spain: analysis of the Spanish National Hospital Discharge Data (2010–2013)

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ABSTRACT

Objective: To describe and analyse hospitalisations for adverse drug reactions (ADRs) involving anticoagulants. We also analysed the progress of the reactions over time, the factors related with ADRs.

Design: A retrospective, descriptive, epidemiological study.

Setting: This study used the Spanish National Hospital Discharge Database (Conjunto Mínimo Básico de Datos, CMBD), over a 4-year period.

Participants: We selected CMBD data corresponding to hospital discharges with a diagnosis of ADRs to anticoagulants (International Classification of Diseases-Ninth Revision, Clinical Modification (ICD-9-CM) code E934.2) in any diagnostic field during the study period.

Main outcome measures: We calculated the annual incidence of ADRs to anticoagulants according to sex and age groups. The median lengths of hospital stay and in-hospital mortality (IHM) were also estimated for each year studied. Bivariate analyses of the changes in variables according to year were based on Poisson regression. IHM was analysed using logistic regression models. The estimates were expressed as ORs and their 95% CI.

Results: During the study period, 50 042 patients were hospitalised because of ADRs to anticoagulants (6.38% of all ADR-related admissions). The number of cases increased from 10 415 in 2010 to 13 891 in 2013. Cumulative incidence of ADRs to anticoagulants was significantly higher for men than women and in all age groups. An adjusted multivariate analysis revealed that IHM did not change significantly over time. We observed a statistically significant association between IHM and age, with the highest risk for the ≥ 85 age group (OR 2.67; 95% CI 2.44 to 2.93).

Conclusions: The incidence of ADRs to anticoagulants in Spain increased from 2010 to 2013, and was significantly higher for men than women and in all age groups. Older patients were particularly susceptible to being hospitalised with an adverse reaction to an anticoagulant.

Strengths and limitations of this study

- The strength of our investigation lies in its large sample size, its 4-year follow-up period and its standardised methodology.
- The second strength is that it has previously been used to investigate adverse drug reaction (ADR)-related hospital admissions in Spain and elsewhere.
- A limitation of this study is that the possibility that ADR-related hospitalisations also include cases in which the ADR occurred during admission.

INTRODUCTION

Adverse drug reactions (ADRs) are a major health problem owing to their impact on morbidity and mortality. The WHO has defined an ADR as ‘any response to a drug which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function.’¹ Investigators have performed numerous studies to estimate the incidence of ADRs and have found that between 1.3% and 11.1% of all hospital admissions are due to ADRs.^{2–7} The importance of ADRs was highlighted by the fact that since Lazarou *et al*⁸ concluded that the incidence of fatal ADRs in US hospitals was extremely high (0.31% of all hospitalisations in the late 1990s), other authors have found that hospital mortality resulting from ADRs ranges from 4.3% to 10.2%.^{5 9–12}

Research on ADRs also attempts to identify which drugs are most commonly associated with the onset of reactions. Anticoagulants are frequently involved in ADRs requiring hospitalisation.^{11–17} This circumstance is reflected in several studies, such as that

carried out in the Netherlands by Ruiter *et al*² among individuals aged ≥ 55 years, which showed that almost 23% of hospital admissions for ADRs were associated with anticoagulants, and that carried out on elderly patients in France, showed that 25.8% of hospitalisations for ADRs involved anticoagulants.¹¹ Anticoagulants have marked innate toxicity, and oral anticoagulants in particular require close monitoring to ensure safe use. The vitamin K antagonists (VKAs) like warfarin are highly effective in treating and preventing thrombosis, but despite its prolific use, these anticoagulants have several disadvantages. These include a narrow therapeutic index, delayed onset and offset of effect, multiple drug interactions, and requirements for monitoring and high-quality dose management.¹³ In addition, anticoagulants are often used in elderly persons^{14–16} and patients with heart problems,^{17–19} who are more susceptible to ADRs.

The objectives of this study are to describe and analyse hospitalisations for ADRs involving anticoagulants based on data from a national hospital discharge database over a 4-year period. We also analyse the progress of the reactions over time, the factors associated with ADRs, and in-hospital outcomes such as in-hospital mortality (IHM) and length of hospital stay.

METHODS

Definition

According to Spanish legislation, ADRs are noxious and unintended response to drugs. They are considered serious when they are lethal or can be life threatening, are the cause of a defect or congenital malformation, can cause significant or lasting disability or can cause or prolong hospitalisation.

Setting

We performed a retrospective, descriptive, epidemiological study using the Spanish National Hospital Discharge Database (Conjunto Mínimo Básico de Datos, CMBD), which is managed by the Spanish Ministry of Health, Social Services and Equality. The database compiles all public and private hospital data, thus enabling it to cover more than 95% of hospital discharges.¹⁹ The CMBD includes patient variables (sex, date of birth), admission date, discharge date, up to 14 discharge diagnoses, and up to 20 procedures performed during the hospital stay. The characteristics of all hospital admissions are registered by medical doctors on the basis of hospital discharge letters and coded by professional coding clerks. The Spanish Ministry of Health, Social Services and Equality sets standards for recordkeeping and performs periodic audits.²⁰ Data collected between 1 January 2010 and 31 December 2013 were analysed. Disease and procedure criteria were defined according to the International Classification of Diseases-Ninth Revision, Clinical Modification (ICD-9-CM),²¹ which is used in the Spanish CMBD.

We selected CMBD data corresponding to hospital discharges with a diagnosis of ADRs to anticoagulants (ICD-9-CM code E934.2 (coumarin, phenindione, heparin, prothrombin synthesis inhibitors and warfarin)) in any diagnostic field during the study period. Other adverse events (eg, accidents, suicides, accidental overdose and dosing errors) were excluded. The median length of hospital stay and IHM were also estimated for each year studied.

Clinical characteristics included information on overall comorbidity at the time of diagnosis, which was assessed using the Charlson comorbidity index (CCI). The index includes 17 categories of comorbid disease, the scores of which are added to obtain an overall score for each patient.²²

Data analysis

A descriptive statistical analysis was performed. Depending on their type and distribution, variables were described using percentages, mean with SD and median with IQR. Bivariate analyses of the changes in variables according to year were based on Poisson regression (relative change for incidence by year of discharge), Pearson's χ^2 test (percentages), analysis of variance (means), and the Kruskal-Wallis test (medians). Interactions have been checked according to sex. No sex interaction was found.

We calculated the annual age-specific incidence by dividing the number of cases per year per age group by the corresponding number of people in that population group using data from the National Institute of Statistics reported on 31 December each year.²³ We also assessed the number of ADRs to anticoagulants among hospitalised patients and expressed this as a percentage of all hospital admissions in Spain between 2010 and 2013. In addition, we assessed the number of ADRs to anticoagulants among hospitalised patients with respect to the total number of prescriptions for this drug group in Spain between 2010 and 2013. Data on dispensed medical products were obtained from the *National Health Prescription Register of the Spanish Ministry of Health, Social Services and Equality*.²⁴ Data from this database were selected at the pharmacological subgroup level B01A code (excluding B01AE and B01AF codes), according to the Anatomical Therapeutic Chemical (ATC) classification system. All data were grouped, thus preventing identification of individual patients.

In order to test the time trend for IHM, logistic regression analyses were performed with mortality as a binary outcome using year of discharge, sex, age and CCI as independent variables. The estimates were expressed as ORs and their 95% CI.

Statistical analyses were performed using Stata V.14.0 (Stata Corp LP, College Station, Texas, USA). Statistical significance was set at $p < 0.05$ (two-tailed).

Ethical aspects

Data confidentiality was maintained at all times according to Spanish legislation. Patient identifiers were deleted before the database was provided to the authors

in order to maintain patient anonymity. It is not possible to identify patients at the individual level in this article or in the database. Given the anonymous and mandatory nature of the data set, it was not necessary to obtain informed consent.

RESULTS

During the 4-year study period, 50 042 individuals were hospitalised with an ADR to an anticoagulant as their primary or secondary diagnosis (6.38% of all ADR-related admissions (50 042/784 635)). **Figure 1** shows the total number of hospitalisations associated with ADRs to anticoagulants during the study period, taking into account the corresponding number of people in that population group, all hospital admissions in Spain between 2010 and 2013, and total number of prescriptions dispensed during this period. Irrespective of the numerator used, an increase in the incidence of hospitalisations with ADRs to anticoagulants can be observed.

The principal characteristics of the study population are summarised in **table 1**. Mean age was 79.4 ± 9.5 years, and most of the patients (52.6%) were women. CCI increased from 1.61 to 1.74 during the study period. Patients hospitalised with an ADR to anticoagulants had high frequency of medical conditions such as atrial fibrillation (AF; 63.16%), congestive heart failure (40.39%),

chronic obstructive pulmonary disease (30.24%), diabetes and renal disease. The median length of stay fell from 8 (IQR=3) days in 2010 to 7 (IQR=2) days in 2013 ($p=0.00$). IHM varied little during the study period (from 10% in 2010 to 10.2% in 2013).

Table 2 shows the annual hospital discharge rates for patients with an ADR to anticoagulants by sex and age group. The cumulative incidence of discharges increased from 22.3 cases per 100 000 inhabitants in 2010 to 29.8 cases per 100 000 inhabitants in 2013 (ie, a 24.9% increase). Cumulative incidence was significantly higher for men than women and in all age groups, although the main increases were observed in the older age groups (26.30% in patients aged ≥ 85 years; $p < 0.05$). The most frequent primary diagnoses and procedures most commonly associated with ADRs according to IHM are summarised in **table 3**. It is noteworthy that 20.6% of patients who died during their hospitalisation had a primary diagnosis of cardiovascular disease (ICD-9 codes 428, 402.91, 428.1, 404.91, 415.19, 428.9, 410.71, 411.1 and 428.23) and 16.8% had a primary diagnosis of bleeding (ICD-9 codes 729.92, 578.9, 578.1, 569.3, 431, 38.9, 599.71, 562.12, 599.7, 784.7, 786.3, 285.1 and 578), intracranial haemorrhage has been the most frequent diagnosis (5.23%), followed by blood vessel puncture (4.15%). The most frequent procedure administered during admission was blood transfusion (18.8%).

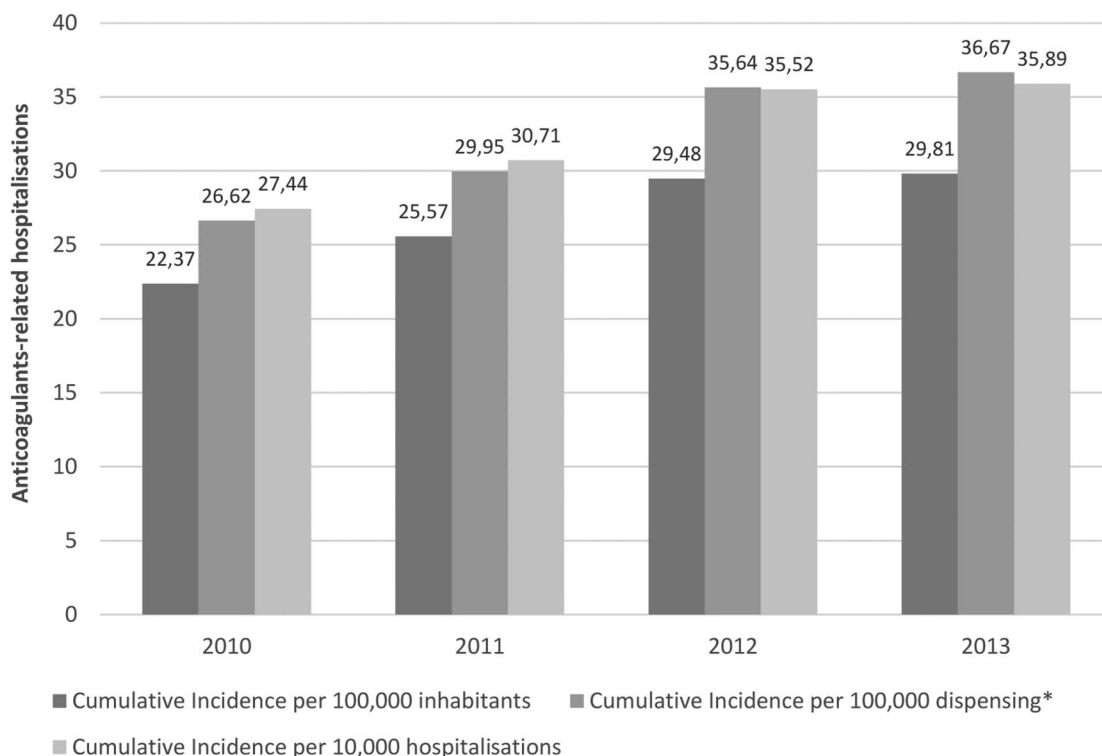


Figure 1 ADRs to anticoagulant in Spain during the period 2010–2013. National Hospital Discharge Database (CMBD).

*Number of prescriptions dispensed BO1A ATC code (except B01AE and B01AF): 39 118 749 (year 2010); 39 899 992 (year 2011); 38 674 897 (year 2012) and 37 877 714 (year 2013). ADR, adverse drug reaction; ATC, Anatomical Therapeutic Chemical; CMBD, Conjunto Mínimo Básico de Datos.

Table 1 Baseline characteristics of ADRs to anticoagulants in Spain during the period 2010–2013

	2010 N (%)	2011 N (%)	2012 N (%)	2013 N (%)	Total N (%)	p Value
Female	5509 (52.89)	6264 (52.41)	7287 (52.86)	7304 (52.58)	26 364 (52.68)	0.857
Age, mean (SD)	78.92 (9.6)	79.24 (9.56)	79.66 (9.48)	79.81 (9.51)	79.45 (9.54)	<0.0001
Charlson comorbidity index, mean (SD)	1.61 (1.07)	1.64 (1.08)	1.68 (1.09)	1.74 (1.09)	1.67 (1.09)	<0.0001
Myocardial infarction	547 (5.25)	610 (5.1)	649 (4.71)	580 (4.18)	2386 (4.77)	<0.0001
Congestive heart failure	3987 (38.28)	4581 (38.33)	5697 (41.33)	5949 (42.83)	20 214 (40.39)	<0.0001
Peripheral vascular disease	537 (5.16)	659 (5.51)	743 (5.39)	810 (5.83)	2749 (5.49)	0.131
Cerebrovascular disease	1225 (11.76)	1410 (11.8)	1546 (11.22)	1645 (11.84)	5826 (11.64)	0.332
Dementia	478 (4.59)	560 (4.69)	686 (4.98)	666 (4.79)	2390 (4.78)	0.524
Chronic pulmonary disease	3070 (29.48)	3562 (29.81)	4181 (30.33)	4319 (31.09)	15 132 (30.24)	0.032
Connective tissue disease— rheumatic disease	248 (2.38)	256 (2.14)	275 (1.99)	329 (2.37)	1108 (2.21)	0.102
Peptic ulcer disease	188 (1.81)	181 (1.51)	216 (1.57)	174 (1.25)	759 (1.52)	0.006
Mild liver disease	415 (3.98)	444 (3.72)	523 (3.79)	567 (4.08)	1949 (3.89)	0.403
Diabetes without chronic complication	2650 (25.44)	3104 (25.97)	3512 (25.48)	3623 (26.08)	12 889 (25.76)	0.541
Diabetes with chronic complication	290 (2.78)	327 (2.74)	423 (3.07)	450 (3.24)	1490 (2.98)	0.059
Hemiplegia or paraplegia	111 (1.07)	150 (1.26)	187 (1.36)	199 (1.43)	647 (1.29)	0.075
Renal disease	2194 (21.07)	2672 (22.36)	3290 (23.87)	3552 (25.57)	11 708 (23.4)	<0.0001
Cancer	487 (4.68)	650 (5.44)	727 (5.27)	718 (5.17)	2582 (5.16)	0.064
Moderate or severe liver disease	94 (0.9)	115 (0.96)	140 (1.02)	143 (1.03)	492 (0.98)	0.752
Metastatic carcinoma	260 (2.5)	316 (2.64)	333 (2.42)	365 (2.63)	1274 (2.55)	0.597
AIDS/HIV	11 (0.11)	14 (0.12)	12 (0.09)	17 (0.12)	54 (0.11)	0.819
Atrial fibrillation	6441 (61.84)	7450 (62.34)	8792 (63.78)	8924 (64.24)	31 607 (63.16)	<0.0001
Thromboembolism	281 (2.7)	283 (2.37)	325 (2.36)	335 (2.41)	1224 (2.45)	0.308
Hypertension	4156 (39.9)	4835 (40.46)	5618 (40.75)	5452 (39.25)	20 061 (40.09)	0.059
Anaemia	3147 (30.22)	3513 (29.4)	4180 (30.32)	4107 (29.57)	14 947 (29.87)	0.279
Surgery	689 (6.62)	748 (6.26)	774 (5.61)	818 (5.89)	3029 (6.05)	0.007
Red cell transfusion	2063 (19.81)	2339 (19.57)	2678 (19.43)	2360 (16.99)	9440 (18.86)	<0.0001
In-hospital mortality	1042 (10)	1205 (10.08)	1491 (10.82)	1424 (10.25)	5162 (10.32)	0.134
LOSH, median (IQR)	8 (5–13)	7 (4–13)	7 (4–12)	7 (4–12)	8 (4–13)	<0.0001

ADR, adverse drug reaction.

An adjusted multivariate analysis (table 4) revealed that IHM did not change significantly over time. We observed a statistically significant association between IHM and age, with the highest risk for the ≥ 85 age group (OR 2.67; 95% CI 2.44 to 2.93).

A higher CCI was associated with a higher risk of death during admission (OR 1.21; 95% CI 1.18 to 1.25). Other factors associated with higher IHM were having a blood transfusion administered, whereas having AF (OR 0.88; 95% CI 0.83 to 0.94) as a diagnosis showed a protective effect.

DISCUSSION

Oral anticoagulants are often associated with ADRs requiring admission to hospital.^{15 17 25} Using data from the CMBD, we found that between 2010 and 2013, a total of 50 042 hospitalisations in Spain were with an ADR to anticoagulant drugs (ie, 6.38% of all hospitalisations with ADRs). This information is consistent with the 7.5% reported for anticoagulants in a study covering the

period 2001–2006 to estimate the burden of ADR-related hospitalisations in Spain.⁹ The values we report are lower than those found in the 5-year study performed by Ruiter *et al*² in the Netherlands, in which 23% of ADR-related hospital admissions in individuals aged ≥ 55 years were associated with anticoagulants. Our results are also lower than the 18.3% frequency of adverse reactions to anticoagulants reported in a recent German study on the impact of ADR-related admissions to internal medicine departments, although the study period was shorter than ours.²⁶ The results of our study show an increase in the incidence of ADR-related hospitalisations during the study period, irrespective of whether the numerator is the general population, the number of hospital admissions or the number of prescriptions of anticoagulants. All three options are suitable for a qualitative analysis to identify the age groups at greatest risk. In addition, the high proportion of elderly patients, with more frequent comorbidity and polypharmacy, is consistent with data from other studies.^{7 14}

Table 2 Incidence of ADRs to anticoagulants according to sex and age groups

	2010		2011		2012		2013		Total		Relative change	
	N	Incidence	N	Incidence	N	Incidence	N	Incidence	N	Incidence	Per cent	Per cent
Male												
<75 years*	1441	6.72	1563	7.29	1694	7.92	1689	7.95	6387	7.47	15.47	15.47
75–84 years	2368	190.52	2739	215.77	3124	243.30	3123	243.45	11 354	223.54	21.74	21.74
>85 years*	1097	331.61	1385	392.03	1680	452.69	1775	450.67	5937	409.71	26.42	26.42
Total*	4906	21.32	5687	24.65	6498	28.18	6587	28.72	23 678	25.72	25.77	25.77
Female												
<75 years*	1026	4.87	1127	5.34	1168	5.53	1224	5.81	4545	5.39	16.18	16.18
75–84 year*s	2582	146.53	2905	162.47	3363	186.85	3250	181.66	12 100	169.49	19.34	19.34
>85 years*	1901	265.79	2232	295.52	2756	351.54	2830	344.56	9719	315.98	25.04	25.04
Total*	5509	23.39	6264	26.47	7287	30.73	7304	30.87	26 364	27.87	24.23	24.23
Total												
<75 years*	2467	5.80	2690	6.32	2862	6.73	2913	6.89	10 932	6.43	15.82	15.82
75–84 years*	4950	164.72	5644	184.60	6487	210.35	6373	207.46	23 454	191.96	20.6	20.6
>85 years*	2998	286.60	3617	326.27	4436	384.04	4605	378.95	15 656	346.00	26.30	26.30
Total*	10 415	22.37	11 951	25.57	13 785	29.48	13 891	29.81	50 042	26.81	24.96	24.96

National Hospital Discharge Database (CMBD).

 Cumulative incidence per 100 000 inhabitants. Cumulative incidence was calculated using the Spanish National Statistics Institute census projections.²²

 *p<0.05 (comparison by year: Poisson regression model for incidence rates, Pearson's χ^2 for proportions).

ADR, adverse drug reaction; CMBD, Conjunto Mínimo Básico de Datos.

Female sex is a recognised risk factor for adverse reactions to specific groups of drugs.^{2 7 27 28} If we focus on the safety profile of anticoagulant drugs, we find that the potential sex differences in the onset of adverse reactions have also been analysed in several meta-analyses, with varying results.^{29–31} However, in our study, sex as a risk factor behaved differently. During the 4-year study period, we observed an increase in the incidence of anticoagulant-related hospitalisations, which was greater in men than in women for all age groups. These data are consistent with those reported by Rodenburg *et al*,³² whose objective was to identify possible differences in ADRs to cardiovascular drugs between men and women over a 6-year period. The authors found that admissions for ADRs to anticoagulants and salicylates were more common in men (RR 0.94; 95% CI 0.90 to 0.98). In recent years, it has become clear that women and men differ in their response to anticoagulant drugs, as shown in the study by Blanco-Molina *et al*³³ in Spain, in which analysis of a sample of 47 499 patients with venous thromboembolism showed that the outcome of therapy with anticoagulants could vary depending on the sex of the patient. Similarly, a recent study in primary care performed by Precioso Costa *et al*³⁴ to determine the degree of control and adherence to therapy in a sample of patients treated with acenocoumarol found that poor control of the international normalised ratio was more common among men (2.77±0.11) than among women (2.66±0.08; p<0.05).

Our analysis of the CMBD registers showed that most patients hospitalised for ADRs to anticoagulants were elderly persons aged 79.45±9.54 years with various clinical conditions such as congestive heart failure and AF, which increase the vulnerability of this group to anticoagulant-induced ADRs. Our results show that the severity of the underlying disease, as expressed by the CCI (1.67±1.09), was high in patients admitted to hospital with anticoagulant-induced reactions; this finding is consistent with those of the study of Alexopoulou *et al*³⁵ in Greece, where patients who had been hospitalised for ADRs had more comorbid conditions (CCI 1.7) than patients admitted for other reasons. Nevertheless, we must not forget that having multiple comorbidities is associated with polypharmacy,¹² as described in a recent study performed in France by Olivier *et al*¹¹ in patients aged ≥65 years and in whom the number of drugs taken was a risk factor for ADR-associated hospitalisations (OR 1.18; 95% CI 1.08 to 1.29).

Oral anticoagulants are the most effective therapy for the prevention of ischaemic stroke and systemic embolism related to AF. During the previous decade, the number of patients who received treatment with oral anticoagulants has increased, mainly owing to the higher number of elderly patients with AF,^{36 37} for whom this therapy is indicated in order to prevent cerebrovascular accidents.³⁸ Analysis of primary diagnoses associated with ADRs to anticoagulants among

Table 3 Most frequent primary diagnoses and procedures among ADRs to anticoagulants according to in-hospital mortality in Spain, 2010–2013

Primary diagnosis (ICD-9 codes)	Outcome					
	Survival to hospital discharge (N, %)		Died during admission (N, %)		Total (N, %)	
Cardiovascular disease (428, 402.91, 428.1, 404.91, 415.19, 428.9, 410.71, 411.1, 428.23)	8196	18.26	1068	20.69	9264	18.51
Bleeding (729.92, 578.9, 578.1, 569.3, 431, 38.9, 599.71, 562.12, 599.7, 784.7, 786.3, 285.1, 578)	6530	14.55	870	16.85	7400	14.79
Respiratory disease (519.8, 491.21, 518.81, 466, 518.84, 491.22, 494.1, 493.92)	5764	12.84	490	9.49	6254	12.5
Pneumonias (486, 507, 481)	3257	7.26	425	8.23	3682	7.36
Renal disease (599, 584.9)	1868	4.16	237	4.59	2105	4.21
Anaemia (280, 280.9, 285.9)	942	2.1	41	0.79	983	1.96
Atrial fibrillation (427.31)	800	1.78	37	0.72	837	1.67
Procedures						
Surgery	2657	5.92	372	7.21	3029	6.05
Red cell transfusion	8416	18.75	1024	19.84	9440	18.86

National Hospital Discharge Database (CMBD).

ADR, adverse drug reaction; CMBD, Conjunto Mínimo Básico de Datos; ICD-9, International Classification of Diseases-Ninth Revision.

Table 4 Multivariate analysis of the factors associated with IHM for all participants with ADRs to anticoagulants in Spain, from 2010 to 2013

	OR (CI 95%)
Age groups (years)	
<75	1
75–84	1.65 (1.50 to 1.80)
≥85	2.67 (2.44 to 2.93)
Sex	
Male	1
Female	0.99 (0.93 to 1.05)
Charlson comorbidity index	1.21 (1.18 to 1.25)
Red cell transfusion	
No	1
Yes	1.09 (1.01 to 1.17)
Atrial fibrillation	
No	1
Yes	0.88 (0.83 to 0.94)
Years	
2013	1
2012	1.08 (0.99 to 1.06)
2011	1.01 (0.93 to 1.10)
2010	1.02 (0.94 to 1.11)

National Hospital Discharge Database (CMBD).

Calculated using logistic regression models: OR. The logistic regression multivariate models were built using 'death (yes/no)' as dependent variables.

ADR, adverse drug reaction; CMBD, Conjunto Mínimo Básico de Datos; IHM, in-hospital mortality.

hospitalised patients reveals that the primary diagnosis was cardiovascular disease in 18.5% of cases and AF in 1.67% of cases, thus potentially explaining why these patients were receiving treatment with anticoagulants. Other diagnoses, such as bleeding (14.79%) and blood transfusion (18.86%) could indicate the reason why patients were hospitalised or what happened during

hospitalisation. Finally, although not associated with anti-coagulant drugs, primary diagnoses such as renal insufficiency (4.21%) could be considered a risk factor if the patient's consumption of anticoagulants is high.

With respect to bleeding as the main diagnosis, our results are consistent with those of studies that associate this diagnosis as the main adverse reaction to anticoagulants. Piazza *et al*¹⁵ performed a 5-year retrospective study to determine the clinical characteristics, types and outcomes of adverse events associated with anticoagulant drugs and found that 25% of adverse reactions comprised bleeding events and that 17% required transfusion of at least one unit of packed red blood cells. However, it is important to remember that the predictors of bleeding in patients undergoing treatment with anticoagulants are mainly clinical factors that include uncontrolled hypertension, a history of myocardial infarction or ischaemic heart disease, cerebrovascular disease, anaemia or a history of bleeding, and concomitant use of other drugs such as antiplatelet agents.³⁹

Patients admitted for adverse reactions to anticoagulants often die, usually because of the profile of patients taking these drugs (eg, old age, comorbidity and polypharmacy).⁴⁰ We found that the IHM associated with adverse reactions to anticoagulants remained constant throughout the study period, with values close to 10%, which were higher than the 6.9% reported by Heng *et al*²⁵ based on the data from the French Database Programme de Médicalisation des Systèmes d'Information (PMSI), including patients aged >75 years.

In contrast with results from other studies, where fatal ADRs seem mainly to affect women,¹² IHM did not seem to be affected by sex in our study.

Our multivariate analysis showed that individuals aged ≥85 years who were admitted to hospital with adverse reactions to anticoagulants are twice as likely to die as

those aged <75 years (OR 2.67; 95% CI 2.44 to 2.93). Similarly, the CCI acts as a predictor of IHM in this age group, since comorbidity worsens the patient's clinical status in the case of an adverse reaction to anticoagulants. In this context, it is noteworthy that AF, the most common significant cardiac arrhythmia, is associated with substantial morbidity from stroke and thromboembolism. According to data from the OFRECE study, which analysed the prevalence of AF in Spain, the prevalence of AF in patients aged >80 years is high (17.7%).³⁷ AF is also associated with increased mortality,⁴¹ although our data analysis revealed that a diagnosis of AF is not a risk factor for IHM in patients admitted for adverse reactions to anticoagulants (OR 0.88; 95% CI 0.83 to 0.94). We have analysed three groups: patients without AF, patients with AF as comorbidity and patients with AF as the primary diagnosis. It can be observed that IHM values are similar between patients without AF and patients presenting AF as a comorbidity (10.5% vs 10.4%). Patients with AF as a primary diagnosis have much lower IHM (~4.4% vs 10%). Patients with AF as the first diagnosis are more frequently women (65.7% vs 47.9% and 55.2% among those without AF and with AF as a comorbidity, respectively), with a mean age between the other two groups (78.7 vs 76.8 years among those without AF and 81.1 years among those with AF as a comorbid condition) and with a mean Charlson index lower than the other two groups (1.5 vs 1.63 and 1.7).

This finding could be associated with the type of treatment of the disease in this patient group. VKA have long been the only available oral anticoagulant for prevention of the thromboembolic complications of AF. These drugs are clearly efficacious, with a relative reduction in the risk of ischaemic stroke in elderly patients. However, the clinical challenge of these drugs is to reach an optimal degree of protection under strict supervision owing to their narrow therapeutic margin, interactions with other drugs and the need for strict control of the degree of anticoagulation. Many patients on treatment with VKA spend time outside of the therapeutic range. Some recently published studies in Spain stress on the high percentage of patients who are not well controlled with VKAs. These values range from 41.5% to 43.7%, according to the results of the CALIFA study,⁴² and the ANFAGAL study⁴³ the prevalence of poorly controlled VKA anticoagulation in Spain in patients with non-valvular AF.

Newly developed anticoagulant agents, such as the direct thrombin inhibitor dabigatran etexilate and the direct factor X inhibitors rivaroxaban and apixaban and edoxaban were recently shown to have a favourable risk-benefit ratio under various clinical conditions where anticoagulants are indicated, as is the case with AF.⁴⁴ The meta-analysis conducted by Ruff *et al*⁴⁵ to assess the relative benefit of new oral anticoagulants in randomised trials in patients with AF, showed that the new oral anticoagulants also significantly reduce all-cause mortality (0.90, 0.85 to 0.95; $p=0.0003$).

Strengths and limitations

Our study has both strengths and limitations. The main strength lies in the large sample size and standardised methodology, which was maintained throughout the study period and has previously been used to investigate ADR-related hospital admissions in Spain and elsewhere.^{9 16 26} We believe that the length of the study period and the exhaustive data provided by the CMBD provide sufficient internal validity, which, in quantitative terms, is seen in the constant frequency of episodes detected every year and, in qualitative terms, in the identification of the age groups at the greatest risk.

Nevertheless, our study is subject to limitations. Given that our findings are based on the diagnosis at discharge, the cumulative incidence of ADRs to anticoagulants among hospitalised patients is probably substantially underestimated. Another limitation is the possibility that ADR-related hospitalisations also include cases in which the ADR occurred during admission, although in our opinion, the possibility that an adverse reaction to an anticoagulant during admission is coded as the main diagnosis seems very low. Furthermore, as a consequence of the study design, we were not able to verify whether the patient was already taking an anticoagulant or whether the reaction resulted from taking an anticoagulant during admission. The Spanish National Hospital Discharge Database (CMBD), includes no data regarding patient treatments or drug consumption. Spanish CMBD does not include data regarding the time of start of treatment with anticoagulants before the adverse reaction appeared. Consequently, it has not been possible for us to include any data in the polymedication analysis that would allow us to assess drug interactions with anticoagulants. In addition, we were unable to specify which specific anticoagulant or type of anticoagulant the patient took. We were unable to identify in detail the specific pharmacological classes involved in ADRs to anticoagulants among hospitalised patients.

CONCLUSIONS

In conclusion, during the study period, 50 042 individuals were hospitalised in Spain for adverse reactions to anticoagulants.

Cumulative incidence increased during this time and was significantly higher for men than women and in all age groups. Older patients were particularly susceptible to being hospitalised with an adverse reaction to an anticoagulant. Our results strongly suggest that individuals >75 years of age with a high CCI had a higher risk of death during admission.

Oral anticoagulant therapy is complex due to the need for control and the haemorrhagic risk the therapy entails. The use of anticoagulants requires custom management and proper selection of treatments, since many of these patients have multiple comorbidities and polypharmacy and some anticoagulants have a high percentage of drug interactions.

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