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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-013224
Article Type:	Research
Date Submitted by the Author:	27-Jun-2016
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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Public health, Pharmacology and therapeutics
Keywords:	Adverse Drug Reactions, anticoagulants, National Hospital Discharge Data

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ABSTRACT

Objective: To describe and analyze hospitalizations for Adverse drug reactions (ADRs) involving anticoagulants. We also analyze the progress of the reactions over time, the factors related with ADRs

Design: Retrospective, descriptive, epidemiologic study

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

Participants: We selected CMBD data corresponding to hospital discharges with a diagnosis of ADRs to anticoagulants (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 length of hospital stay and in-hospital mortality were also estimated for each year studied. Bivariate analyses of the changes in variables according to year were based on Poisson regression. In-hospital mortality was analyzed using logistic regression models. The estimates were expressed as odds ratios (OR) and their 95% confidence interval (95% CI).

Results: During the study period, 50,042 patients were hospitalized 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, 2.44-2.93).

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 hospitalized with an adverse reaction to an anticoagulant.

STRENGTHS AND LIMITATIONS

- The strength of our investigation lies in its large sample size, its 4-year follow-up period and its standardized methodology.
- The second strength is that has previously been used to investigate ADR-related hospital admissions in Spain and elsewhere.
- A limitation of this study is that the possibility that ADR-related hospitalizations 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 World Health Organization 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 hospitalizations 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 hospitalization[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, which showed that 25.8% of hospitalizations 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 (VKA) like warfarin are highly effective in treating and preventing thrombosis, but despite its prolific use, these anticoagulants have got many 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[14,15,16] and patients with heart problems[17, 18,19], who are more susceptible to ADRs.

The objectives of this study are to describe and analyze hospitalizations for ADRs involving anticoagulants based on data from a national hospital discharge database over a 4-year period. We also analyze 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

Setting

We performed a retrospective, descriptive, epidemiologic study using the Spanish National Hospital Discharge Database (CMBD, Conjunto Mínimo Básico de Datos), 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 January 1, 2010 and December 31, 2013 were analyzed. 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[23].

Data Analysis

A descriptive statistical analysis was performed. Depending on their type and distribution, variables were described using percentages, mean with standard deviation, and median with interquartile range (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 chi-square test (percentages), ANOVA (means), and the Kruskal-Wallis test (medians).

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 at December 31 each year[22]. We also assessed the number of anticoagulant-related hospital admissions and expressed this as a percentage of all hospital admissions in Spain between 2010 and 2013. In addition, we assessed the number of anticoagulant-related hospital admissions 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 odds ratios (OR) and their 95% confidence interval (95% CI).

Statistical analyses were performed using Stata version 14.0 (Stata Corp LP, College Station, TX, USA). Statistical significance was set at $p<0.05$ (2-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 dataset, it was not necessary to obtain informed consent.

The study protocol was approved by the Ethics Committee of Universidad Rey Juan Carlos.

RESULTS

During the 4-year study period, 50,042 individuals were hospitalized 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 hospitalizations

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 hospitalizations with ADRs to anticoagulants can be observed.

The principal characteristics of the study population are summarized in table 1. Mean age was 79.4±9.5years, and most patients (52.6%) were women. CCI increase from 1.61 to 1.74 during the study period. Patients hospitalized with a ADRs to anticoagulants had a high frequency of medical conditions such as atrial fibrillation (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 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 In-hospital mortality are summarized in table 3. It is noteworthy that 20.6% of patients who died during their hospitalization 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 hemorrhage

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%).

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, 2.44-2.93).

A higher CCI was associated with a higher risk of death during admission (OR, 1.21; 95%CI, 1.18-1.25). Other factors associated with higher IHM was having a blood transfusion administered, whereas having atrial fibrillation (OR, 0.88; 95%CI, 0.83-0.94) 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 hospitalizations in Spain were with an ADR to anticoagulant drugs (ie, 6.38% of all hospitalizations 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 hospitalizations 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 hospitalizations 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 3 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].

Female sex is a recognized 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 analyzed in several meta-analyses, with varying results[29,30,31]. 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 hospitalizations, 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, 0.90-0.98). 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 normalized 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 hospitalized for ADRs to anticoagulants were elderly persons aged 79.45±9.54 years with various clinical

conditions such as congestive heart failure and atrial fibrillation, 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. in Greece[35], where patients who had been hospitalized 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 hospitalizations (OR, 1.18; 95%CI, 1.08-1.29).

Oral anticoagulants are the most effective therapy for the prevention of ischemic stroke and systemic embolism related to atrial fibrillation. During the last decade, the number of patients who received treatment with oral anticoagulants has increased, mainly owing to the higher number of elderly patients with atrial fibrillation[36,37], for whom this therapy is indicated in order to prevent cerebrovascular accidents[38]. Analysis of primary diagnoses associated with anticoagulant-related hospitalizations reveals that the primary diagnosis was cardiovascular disease in 18.5% of cases and atrial fibrillation 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 hospitalized or what happened during hospitalization. Finally, although not associated with anticoagulant 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 ischemic heart disease, cerebrovascular disease, anemia 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 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, 2.44-2.93). 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 atrial

fibrillation, the most common significant cardiac arrhythmia, is associated with substantial morbidity from stroke and thromboembolism. According to data from the OFRECE study, which analyzed the prevalence of atrial fibrillation in Spain, the prevalence of atrial fibrillation in patients aged >80 years is high (17.7%)[37]. Atrial fibrillation is also associated with increased mortality[41], although our data analysis revealed that a diagnosis of atrial fibrillation is not a risk factor for IHM in patients admitted for adverse reactions to anticoagulants (OR, 0.88; 95%CI, 0.83-0.94). 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 atrial fibrillation. These drugs are clearly efficacious, with a relative reduction in the risk of ischemic 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 VKA, spend time outside of the therapeutic range TTR. Some recently published studies in Spain, stress the high percentage of patients not well controlled with VKAs. These values ranging from 41.5% to 43.7%, according to the results of the CALIFA study[42], and ANFAGAL study[43] the prevalence of poorly controlled vitamin K antagonist anticoagulation in Spain in patients with nonvalvular atrial fibrillation.

Newly developed anticoagulant agents, such as the direct thrombin inhibitor dabigatran etexilate and the direct factor X inhibitors rivaroxaban and apixaban y edoxaban were recently shown to have a favorable risk-benefit ratio in various clinical conditions where anticoagulants are indicated, as is the case with atrial fibrillation[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 atrial fibrillation, showed that the new oral anticoagulants also significantly reduce all-cause mortality (0·90, 0·85–0·95; p=0·0003)

Strengths and limitations

Our study has both strengths and limitations. The main strength lies in the large sample size and standardized 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 anticoagulant-related hospital admissions is probably substantially underestimated. Another limitation is the possibility that ADR-related hospitalizations 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. 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 anticoagulant-related hospital admissions.

CONCLUSIONS

In conclusion, during the study period, 50,042 individuals were hospitalized 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 hospitalized 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 hemorrhagic risk the therapy entails The use of anticoagulants requires a 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.

Acknowledgements

We wish to thank the Spanish Ministry of Health, Social Services and Equality, for providing data.

Contributorship statement: All authors contributed to the conception and design of the study. PCG, RJG originated and designed the study and coordinated the writing of the article. VHB contributed to the analysis of the data and to the drafting of the paper. JEH, IJT, AAM, ALdA, JdMD, JRB and JMR contributed to the interpretation of the results and to the drafting of the paper. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors have seen and approved the final version. PCG is the guarantor.

Funding

This study forms part of research funded by the Daiichi Sankyo España, S.A grant no: 2015/00200/001-A295. The funding source had no involvement in the research process.

Competing interests: None declared.

Data sharing statement: No additional data available

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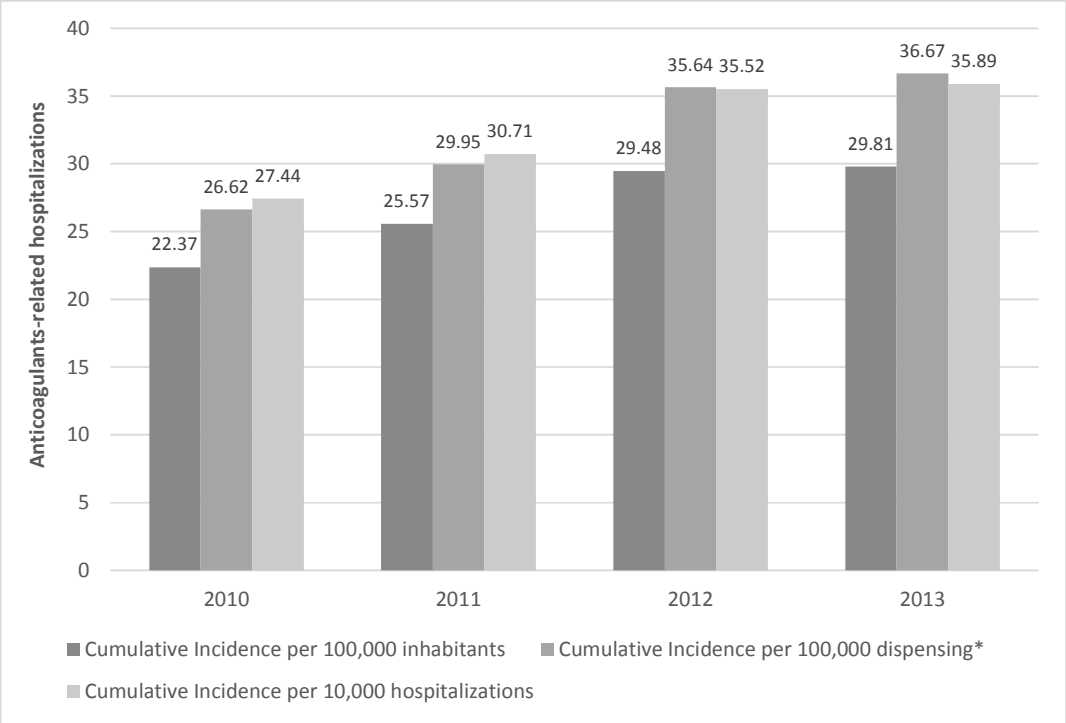
Figure 1. Adverse drug reactions (ADRs) to anticoagulant in Spain during the period 2010-2013. National Hospital Discharge Database (CMBD, Conjunto Mínimo Básico de Datos).



* 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).

Table 1. Baseline characteristics of ADRs to anticoagulants anticoagulant in Spain during the period 2010-2013.

	2010 N (%)	2011 N (%)	2012 N (%)	2013 N (%)	Total N (%)	P-value
Female	5,509(52.89)	6,264(52.41)	7,287(52.86)	7,304(52.58)	2,6364(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)	0.000
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)	0.000
Myocardial infarction	547(5.25)	610(5.1)	649(4.71)	580(4.18)	2,386(4.77)	0.000
Congestive heart failure	3,987(38.28)	4,581(38.33)	5,697(41.33)	5,949(42.83)	2,0214(40.39)	0.000
Peripheral vascular disease	537(5.16)	659(5.51)	743(5.39)	810(5.83)	2,749(5.49)	0.131
Cerebrovascular disease	1,225(11.76)	1,410(11.8)	1,546(11.22)	1,645(11.84)	5,826(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	3,070(29.48)	3,562(29.81)	4,181(30.33)	4,319(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)	1,108(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)	1,949(3.89)	0.403
Diabetes without chronic complication	2,650(25.44)	3,104(25.97)	3,512(25.48)	3,623(26.08)	12,889(25.76)	0.541
Diabetes with chronic complication	290(2.78)	327(2.74)	423(3.07)	450(3.24)	1,490(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	2,194(21.07)	2,672(22.36)	3,290(23.87)	3,552(25.57)	11,708(23.4)	0.000
Cancer	487(4.68)	650(5.44)	727(5.27)	718(5.17)	2,582(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)	1,274(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	6,441(61.84)	7,450(62.34)	8,792(63.78)	8,924(64.24)	31,607(63.16)	0.000
Thromboembolism	281(2.7)	283(2.37)	325(2.36)	335(2.41)	1,224(2.45)	0.308
Hypertension	4,156(39.9)	4,835(40.46)	5,618(40.75)	5,452(39.25)	20,061(40.09)	0.059
Anaemia	3,147(30.22)	3,513(29.4)	4,180(30.32)	4,107(29.57)	14,947(29.87)	0.279
Surgery	689(6.62)	748(6.26)	774(5.61)	818(5.89)	3,029(6.05)	0.007
Red Cell transfusion	2,063(19.81)	2,339(19.57)	2,678(19.43)	2,360(16.99)	9,440(18.86)	0.000
In-hospital mortality	1,042(10)	1,205(10.08)	1,491(10.82)	1,424(10.25)	5,162(10.32)	0.134
LOSH, median (IQR)	8(13)	7(13)	7(12)	7(12)	8(13)	0.000

Table 2: Incidence of ADRs to anticoagulants according to sex and age groups. National Hospital Discharge Database (CMBD, Conjunto Mínimo Básico de Datos).

		2010		2011		2012		2013		Total		Relative Change
		N	Incidence	N	Incidence	N	Incidence	N	Incidence	N	Incidence	%
Male	< 75 years*	1,441	6.72	1,563	7.29	1,694	7.92	1,689	7.95	6,387	7.47	15,47
	75-84 years	2,368	190.52	2,739	215.77	3,124	243.30	3,123	243.45	11,354	223.54	21,74
	≥ 85 years*	1,097	331.61	1,385	392.03	1,680	452.69	1,775	450.67	5,937	409.71	26,42
	Total*	4,906	21.32	5,687	24.65	6,498	28.18	6,587	28.72	23,678	25.72	25,77
Female	< 75 years*	1,026	4.87	1,127	5.34	1,168	5.53	1,224	5.81	4,545	5.39	16,18
	75-84 year*s	2,582	146.53	2,905	162.47	3,363	186.85	3,250	181.66	12,100	169.49	19,34
	≥ 85 years*	1,901	265.79	2,232	295.52	2,756	351.54	2,830	344.56	9,719	315.98	25.04
	Total*	5,509	23.39	6,264	26.47	7,287	30.73	7,304	30.87	26,364	27.87	24,23
Total	< 75 years*	2,467	5.80	2,690	6.32	2,862	6.73	2,913	6.89	10,932	6.43	15,82
	75-84 years*	4,950	164.72	5,644	184.60	6,487	210.35	6,373	207.46	23,454	191.96	20,6
	≥ 85 years*	2,998	286.60	3,617	326.27	4,436	384.04	4,605	378.95	15,656	346.00	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

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 chi-square for proportions).

Table 3. Most frequent primary diagnoses and procedures among ADRs to anticoagulants according to In-hospital mortality in Spain, 2010-2013. National Hospital Discharge Database (CMBD, Conjunto Mínimo Básico de Datos)

	Outcome

Primary diagnosis (ICD-9 codes)	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)	8,196	18.26	1,068	20.69	9,264	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)	6,530	14.55	870	16.85	7,400	14.79
Respiratory disease (519.8, 491.21, 518.81, 466, 518.84, 491.22, 494.1, 493.92)	5,764	12.84	490	9.49	6,254	12.5
Pneumonias (486, 507, 481)	3,257	7.26	425	8.23	3,682	7.36
Renal disease (599, 584.9)	1,868	4.16	237	4.59	2,105	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	2,657	5.92	372	7.21	3,029	6.05
Red Cell transfusion	8,416	18.75	1,024	19.84	9,440	18.86

Table 4. Multivariate analysis of the factors associated with in-hospital mortality (IHM) for all subjects with ADRs to anticoagulants in Spain, from 2010 to 2013. National Hospital Discharge Database (CMBD, Conjunto Mínimo Básico de Datos).

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

OR. Odds Ratio. Calculated using logistic regression models: odds ratio (OR). The logistic regression multivariate models were built using ‘‘death (yes/no)’’ as dependent variables.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6-7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Study size	10	Explain how the study size was arrived at	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*e*) Describe any sensitivity analyses	8

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9,
		(b) Indicate number of participants with missing data for each variable of interest	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

ADVERSE DRUG REACTIONS TO ANTICOAGULANTS IN SPAIN. Analysis of the Spanish National Hospital Discharge Data (2010-2013).

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-013224.R1
Article Type:	Research
Date Submitted by the Author:	27-Sep-2016
Complete List of Authors:	Carrasco-Garrido, Pilar; Rey Juan Carlos Univ, Preventive Medicine and Public Health Teaching and Research Unit Hernández-Barrera , Valentín; Rey Juan Carlos Univ, Preventive Medicine and Public Health Teaching and Research Unit Esteban-Hernandez, Jesus; Rey Juan Carlos Univ, Preventive Medicine and Public Health Teaching and Research Unit Jimenez-Trujillo, Isabel ; Rey Juan Carlos Univ, Preventive Medicine and Public Health Teaching and Research Unit Alvaro, Alejandro; Rey Juan Carlos Univ, Preventive Medicine and Public Health Teaching and Research Unit Lopez-de-Andres, Ana ; Rey Juan Carlos Univ, Preventive Medicine and Public Health Teaching and Research Unit de Miguel-Diez, Javier; Hospital General Universitario Gregorio Marañón Rodríguez-Barrios, José ; Daiichi Sankyo Europe GmbH Muñoz-Robles, Jorge; Daiichi Sankyo España, S.A Jimenez-Garcia, Rodrigo; Rey Juan Carlos Univ, Preventive Medicine and Public Health Teaching and Research Unit
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Public health, Pharmacology and therapeutics
Keywords:	Adverse Drug Reactions, anticoagulants, National Hospital Discharge Data

TITLE: 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 analyze hospitalizations for Adverse drug reactions (ADRs) involving anticoagulants. We also analyze the progress of the reactions over time, the factors related with ADRs

Design: Retrospective, descriptive, epidemiologic study

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

Participants: We selected CMBD data corresponding to hospital discharges with a diagnosis of ADRs to anticoagulants (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 length of hospital stay and in-hospital mortality were also estimated for each year studied. Bivariate analyses of the changes in variables according to year were based on Poisson regression. In-hospital mortality (IHM) was analyzed using logistic regression models. The estimates were expressed as odds ratios (OR) and their 95% confidence interval (95% CI).

Results: During the study period, 50,042 patients were hospitalized 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, 2.44-2.93).

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 hospitalized with an adverse reaction to an anticoagulant.

STRENGTHS AND LIMITATIONS

- The strength of our investigation lies in its large sample size, its 4-year follow-up period and its standardized methodology.
- The second strength is that has previously been used to investigate ADR-related hospital admissions in Spain and elsewhere.
- A limitation of this study is that the possibility that ADR-related hospitalizations 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 World Health Organization 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 hospitalizations 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 hospitalization[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, which showed that 25.8% of hospitalizations 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 (VKA) like warfarin are highly effective in treating and preventing thrombosis, but despite its prolific use, these anticoagulants have got many 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[14,15,16] and patients with heart problems[17, 18,19], who are more susceptible to ADRs.

The objectives of this study are to describe and analyze hospitalizations for ADRs involving anticoagulants based on data from a national hospital discharge database over a 4-year period. We also analyze 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 hospitalization.

Setting

We performed a retrospective, descriptive, epidemiologic study using the Spanish National Hospital Discharge Database (CMBD, Conjunto Mínimo Básico de Datos), 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 January 1, 2010 and December 31, 2013 were analyzed. 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 standard deviation, and median with interquartile range (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 chi-square test (percentages), ANOVA (means), and the Kruskal-Wallis test (medians). Interactions have been checked according 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 at December 31 each year[23]. We also assessed the number of ADRs to anticoagulants among hospitalized 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 hospitalized 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 odds ratios (OR) and their 95% confidence interval (95% CI).

Statistical analyses were performed using Stata version 14.0 (Stata Corp LP, College Station, TX, USA). Statistical significance was set at $p<0.05$ (2-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 dataset, it was not necessary to obtain informed consent.

The study protocol was approved by the Ethics Committee of Universidad Rey Juan Carlos.

RESULTS

During the 4-year study period, 50,042 individuals were hospitalized 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 hospitalizations 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 hospitalizations with ADRs to anticoagulants can be observed.

The principal characteristics of the study population are summarized in table 1. Mean age was 79.4±9.5years, and most patients (52.6%) were women. CCI increase from 1.61 to 1.74 during the study period. Patients hospitalized with a ADRs to anticoagulants had a high frequency of medical conditions such as atrial fibrillation (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 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 In-

hospital mortality are summarized in table 3. It is noteworthy that 20.6% of patients who died during their hospitalization 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 hemorrhage 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%).

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, 2.44-2.93).

A higher CCI was associated with a higher risk of death during admission (OR, 1.21; 95%CI, 1.18-1.25). Other factors associated with higher IHM was having a blood transfusion administered, whereas having atrial fibrillation (OR, 0.88; 95%CI, 0.83-0.94) 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 hospitalizations in Spain were with an ADR to anticoagulant drugs (ie, 6.38% of all hospitalizations 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 hospitalizations 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 hospitalizations 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 3 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].

Female sex is a recognized 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 analyzed in several meta-analyses, with varying results[29,30,31]. 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 hospitalizations, 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, 0.90-0.98). 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 normalized 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 hospitalized for ADRs to anticoagulants were elderly persons aged 79.45±9.54 years with various clinical conditions such as congestive heart failure and atrial fibrillation, 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. in Greece[35], where patients who had been hospitalized 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 hospitalizations (OR, 1.18; 95%CI, 1.08-1.29).

Oral anticoagulants are the most effective therapy for the prevention of ischemic stroke and systemic embolism related to atrial fibrillation. During the last decade, the number of patients who received treatment with oral anticoagulants has increased, mainly owing to the higher number of elderly patients with atrial fibrillation[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 hospitalized patients reveals that the primary diagnosis was cardiovascular disease in 18.5% of cases and atrial fibrillation 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 hospitalized or what happened during hospitalization. Finally, although not associated with anticoagulant 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 ischemic heart disease, cerebrovascular disease, anemia 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 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, 2.44-2.93). 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 atrial fibrillation, the most common significant cardiac arrhythmia, is associated with substantial morbidity from stroke and thromboembolism. According to data from the OFRECE study, which analyzed the prevalence of atrial fibrillation in Spain, the prevalence of atrial fibrillation in patients aged >80 years is high (17.7%)[37]. Atrial fibrillation is also associated with increased mortality[41], although our data analysis revealed that a diagnosis of atrial fibrillation is not a risk factor for IHM in patients admitted for adverse reactions to anticoagulants (OR, 0.88; 95%CI, 0.83-0.94). We have analyzed 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% approx.) Patients with AF as the first diagnosis are more frequently females (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 group (78.7 years 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 groups 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 atrial fibrillation. These drugs are clearly efficacious,

with a relative reduction in the risk of ischemic 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 VKA, spend time outside of the therapeutic range TTR. Some recently published studies in Spain, stress the high percentage of patients not well controlled with VKAs. These values ranging from 41.5% to 43.7%, according to the results of the CALIFA study[42], and ANFAGAL study[43] the prevalence of poorly controlled vitamin K antagonist anticoagulation in Spain in patients with nonvalvular atrial fibrillation.

Newly developed anticoagulant agents, such as the direct thrombin inhibitor dabigatran etexilate and the direct factor X inhibitors rivaroxaban and apixaban y edoxaban were recently shown to have a favorable risk-benefit ratio in various clinical conditions where anticoagulants are indicated, as is the case with atrial fibrillation[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 atrial fibrillation, showed that the new oral anticoagulants also significantly reduce all-cause mortality (0·90, 0·85–0·95; p=0·0003)

Strengths and limitations

Our study has both strengths and limitations. The main strength lies in the large sample size and standardized 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 hospitalized patients is probably substantially underestimated. Another limitation is the possibility that ADR-related hospitalizations 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, Conjunto Mínimo Básico de Datos), 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 hospitalized patients.

CONCLUSIONS

In conclusion, during the study period, 50,042 individuals were hospitalized 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 hospitalized 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 hemorrhagic risk the therapy entails The use of anticoagulants requires a 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.

Acknowledgements

We wish to thank the Spanish Ministry of Health, Social Services and Equality, for providing data.

Contributorship statement: All authors contributed to the conception and design of the study. PCG, RJG originated and designed the study and coordinated the writing of the article. VHB contributed to the analysis of the data and to the drafting of the paper. JEH, IJT, AAM, ALdA, JdMD, JRB and JMR contributed to the interpretation of the results and to the drafting of the paper. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors have seen and approved the final version. PCG is the guarantor.

Funding

This study forms part of research funded by the Daiichi Sankyo España, S.A grant no: 2015/00200/001-A295. The funding source had no involvement in the research process.

Competing interests: None declared.

Data sharing statement: No additional data available

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Table 1. Baseline characteristics of ADRs to anticoagulants anticoagulant in Spain during the period 2010-2013.

	2010 N (%)	2011 N (%)	2012 N (%)	2013 N (%)	Total N (%)	P-value
Female	5,509(52.89)	6,264(52.41)	7,287(52.86)	7,304(52.58)	2,6364(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)	2,386(4.77)	< 0.0001
Congestive heart failure	3,987(38.28)	4,581(38.33)	5,697(41.33)	5,949(42.83)	2,0214(40.39)	< 0.0001
Peripheral vascular disease	537(5.16)	659(5.51)	743(5.39)	810(5.83)	2,749(5.49)	0.131
Cerebrovascular disease	1,225(11.76)	1,410(11.8)	1,546(11.22)	1,645(11.84)	5,826(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	3,070(29.48)	3,562(29.81)	4,181(30.33)	4,319(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)	1,108(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)	1,949(3.89)	0.403
Diabetes without chronic complication	2,650(25.44)	3,104(25.97)	3,512(25.48)	3,623(26.08)	12,889(25.76)	0.541
Diabetes with chronic complication	290(2.78)	327(2.74)	423(3.07)	450(3.24)	1,490(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	2,194(21.07)	2,672(22.36)	3,290(23.87)	3,552(25.57)	11,708(23.4)	< 0.0001
Cancer	487(4.68)	650(5.44)	727(5.27)	718(5.17)	2,582(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)	1,274(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	6,441(61.84)	7,450(62.34)	8,792(63.78)	8,924(64.24)	31,607(63.16)	< 0.0001
Thromboembolism	281(2.7)	283(2.37)	325(2.36)	335(2.41)	1,224(2.45)	0.308
Hypertension	4,156(39.9)	4,835(40.46)	5,618(40.75)	5,452(39.25)	20,061(40.09)	0.059
Anaemia	3,147(30.22)	3,513(29.4)	4,180(30.32)	4,107(29.57)	14,947(29.87)	0.279
Surgery	689(6.62)	748(6.26)	774(5.61)	818(5.89)	3,029(6.05)	0.007
Red Cell transfusion	2,063(19.81)	2,339(19.57)	2,678(19.43)	2,360(16.99)	9,440(18.86)	< 0.0001
In-hospital mortality	1,042(10)	1,205(10.08)	1,491(10.82)	1,424(10.25)	5,162(10.32)	0.134
LOSH, median (IQR)	8(5-13)	7(4-13)	7(4-12)	7(4-12)	8(4-13)	< 0.0001

Table 2: Incidence of ADRs to anticoagulants according to sex and age groups. National Hospital Discharge Database (CMBD, Conjunto Mínimo Básico de Datos).

		2010		2011		2012		2013		Total		Relative Change
		N	Incidence	N	Incidence	N	Incidence	N	Incidence	N	Incidence	%
Male	< 75 years*	1,441	6.72	1,563	7.29	1,694	7.92	1,689	7.95	6,387	7.47	15,47
	75-84 years	2,368	190.52	2,739	215.77	3,124	243.30	3,123	243.45	11,354	223.54	21,74
	≥ 85 years*	1,097	331.61	1,385	392.03	1,680	452.69	1,775	450.67	5,937	409.71	26,42
	Total*	4,906	21.32	5,687	24.65	6,498	28.18	6,587	28.72	23,678	25.72	25,77
Female	< 75 years*	1,026	4.87	1,127	5.34	1,168	5.53	1,224	5.81	4,545	5.39	16,18
	75-84 year*s	2,582	146.53	2,905	162.47	3,363	186.85	3,250	181.66	12,100	169.49	19,34
	≥ 85 years*	1,901	265.79	2,232	295.52	2,756	351.54	2,830	344.56	9,719	315.98	25.04
	Total*	5,509	23.39	6,264	26.47	7,287	30.73	7,304	30.87	26,364	27.87	24,23
Total	< 75 years*	2,467	5.80	2,690	6.32	2,862	6.73	2,913	6.89	10,932	6.43	15,82
	75-84 years*	4,950	164.72	5,644	184.60	6,487	210.35	6,373	207.46	23,454	191.96	20,6
	≥ 85 years*	2,998	286.60	3,617	326.27	4,436	384.04	4,605	378.95	15,656	346.00	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

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 chi-square for proportions).

Table 3. Most frequent primary diagnoses and procedures among ADRs to anticoagulants according to In-hospital mortality in Spain, 2010-2013. National Hospital Discharge Database (CMBD, Conjunto Mínimo Básico de Datos)

	Outcome

Primary diagnosis (ICD-9 codes)	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)	8,196	18.26	1,068	20.69	9,264	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)	6,530	14.55	870	16.85	7,400	14.79
Respiratory disease (519.8, 491.21, 518.81, 466, 518.84, 491.22, 494.1, 493.92)	5,764	12.84	490	9.49	6,254	12.5
Pneumonias (486, 507, 481)	3,257	7.26	425	8.23	3,682	7.36
Renal disease (599, 584.9)	1,868	4.16	237	4.59	2,105	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	2,657	5.92	372	7.21	3,029	6.05
Red Cell transfusion	8,416	18.75	1,024	19.84	9,440	18.86

Table 4. Multivariate analysis of the factors associated with in-hospital mortality (IHM) for all subjects with ADRs to anticoagulants in Spain, from 2010 to 2013. National Hospital Discharge Database (CMBD, Conjunto Mínimo Básico de Datos).

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

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

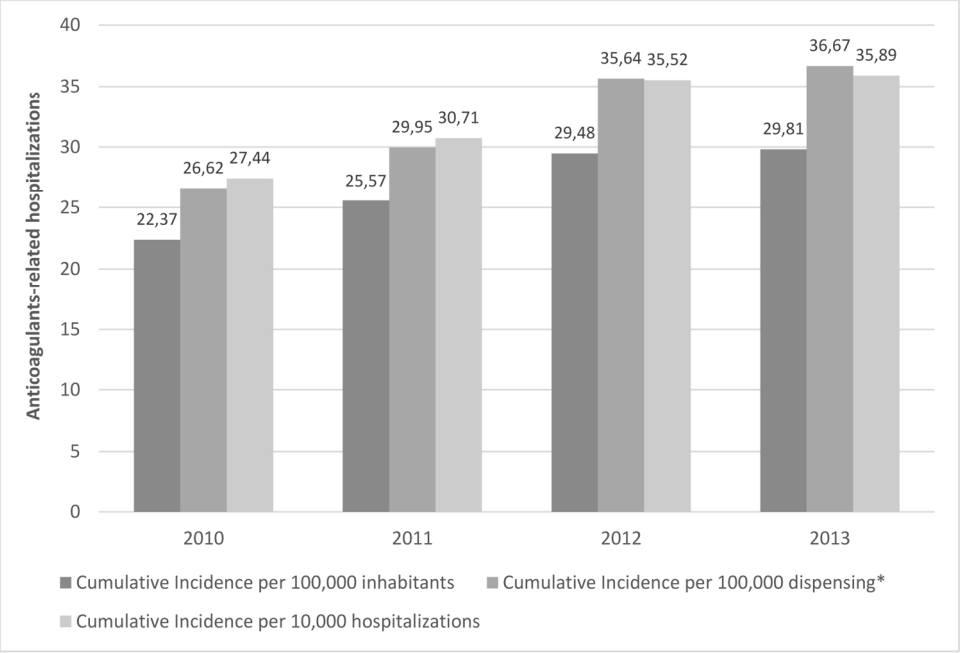

Figure 1. Adverse drug reactions (ADRs) to anticoagulant in Spain during the period 2010-2013. National Hospital Discharge Database (CMBD, Conjunto Mínimo Básico de Datos).
* Number of prescriptions dispensed BO1A ATC code (except B01AE and B01AF): 39,118,749 (year 2010); 39,899,992(year 2011); 38,674,897(year 2012) and 37,877,714 (year 2013).

156x104mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6-7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Study size	10	Explain how the study size was arrived at	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*e*) Describe any sensitivity analyses	8

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9,
		(b) Indicate number of participants with missing data for each variable of interest	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.