Hospital admissions for bleeding events associated with treatment with apixaban, dabigatran and rivaroxaban

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ABSTRACT

Objectives To analyse the hospital admissions for bleeding events associated with treatment with direct oral anticoagulants (DOACs). To describe the characteristics and outcomes of those patients.

Methods A retrospective observational study was carried out in the framework of an integral risk management plan of drugs and proactive pharmacovigilance of hospital admissions for bleeding associated with apixaban, dabigatran and rivaroxaban from April 2015 through December 2016. Cases were identified using the information management tool of Orion Clinic (hospital electronic medical history) and by reviewing the hospital discharge reports. Various biometric, clinical and pharmacotherapeutic variables of each patient were registered.

Results 37 hospitalisation episodes for DOAC-induced bleeding in 32 patients (15 received rivaroxaban, 9 apixaban and 8 dabigatran) were detected, representing an incidence rate of 3.44 per 100 person-years (95% CI 2.35 to 4.86). The most common bleeding site was gastrointestinal (27 cases, 73.0%). Intracranial bleeding was rare (three cases, 8.1%). Four patients (12.5%) were receiving DOACs at full doses and had a ´dose reduction indication'. The mean (SD) length of stay was 8.4 (5.2) days. Three patients (8.1%) died during the hospitalisation. Among bleeding episodes without fatal outcome, DOACs were stopped in 14 cases, continued in 14 cases, switched for another DOAC in two cases and the dose was reduced in four cases.

Conclusions DOACs are associated with serious bleeding events that require hospitalisation. The risk/benefit ratio assessment considering patient preferences and an individualised follow-up, especially in patients who are elderly, polymedicated or have impaired renal function, can help to reinforce the safe use of DOACs.

INTRODUCTION

Cardiovascular diseases with atherothrombotic origin have a considerable impact on the morbidity and mortality of Western society. Oral anticoagulant therapy is used for the management and prevention of deep venous thrombosis and pulmonary embolism, prophylaxis of deep venous thrombosis in patients after surgery and prevention of stroke in patients with atrial fibrillation (AF).

For decades, vitamin K antagonists (VKAs) have been the only available option used to treat the above diseases. Warfarin is the most used VKA worldwide, but in Spain the use of acenocoumarol is significantly higher than that of warfarin.[1] However, non-vitamin oral anticoagulants, also known as direct oral anticoagulants (DOACs), including the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban, apixaban and edoxaban, have been incorporated in clinical practice in recent years. All of them have shown a favourable risk/benefit ratio under various clinical conditions which are approved, as is the case for non-valvular AF.[2–5]

In Spain, the incidence of hospitalisations for adverse effects due to anticoagulants has increased in recent years and intracranial (IC) haemorrhage has been associated as the most frequent diagnosis of bleeding.[6] However, since the marketing of DOACs, very few studies have evaluated the impact on hospital emergencies and admissions owing to bleeding events in patients receiving these drugs.[7–9] Real-world data, particularly those obtained in the context of pharmacovigilance, can help to improve the safe use of DOACs.

This study aims to analyse the hospital admissions for bleeding associated with treatment with DOACs and to describe the characteristics and outcomes of those patients.

METHODS

Study design

A cross-sectional analysis of a retrospective case series of hospital admissions for bleeding events due to treatment with apixaban, dabigatran and rivaroxaban from 1 April 2015 through 31 December 2016 (20 months) was performed. This study was developed in the context of an integral risk management plan of drugs and proactive pharmacovigilance of Francesc de Borja Hospital (Gandia, Valencia, Spain).

Study population

The population assigned to our Health Department and to our hospital is 168 082 inhabitants. Cases were detected by using the information management tool of Orion Clinic (the hospital electronic medical history). The terms 'apixaban', 'dabigatran', 'rivaroxaban', 'Eliquis', 'Pradaxa' and 'Xarelto' were used as search filters on the hospital discharge reports. At least one bleeding diagnosis, based on International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM) coding, was also included at hospital discharge report. We took into account the next ICD-9-CM codes: 280.0, secondary anaemia to chronic blood loss; 285.1, acute

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post-haemorrhagic anaemia; 286.5, haemorrhagic disorder due to anticoagulants; 360.43, haemophthalmos; 372.72, conjunctival haemorrhage; 379.23, vitreous haemorrhage; 423.0, haemopericardium; 430, subarachnoid haemorrhage; 431, intracerebral haemorrhage; 432.9, unspecified intracranial haemorrhage; 459.0, unspecified haemorrhage; 568.81, haemoperitoneum; 569.3, rectal haemorrhage; 578.0, haematemesis; 578.1, melaena; 578.9, unspecified haemorrhage of gastrointestinal tract; 599.7, haematuria; 599.84, urethral bleeding; 719.10, haemarthrosis; 782.7, ecchymosis; 784.7, epistaxis; 786.3, haemoptysis; 922.1, chest wall; 922.2, abdominal wall; and 964.2, poisoning by anticoagulants.

The medical criteria, set out explicitly in the same discharge reports, were considered as sufficient for acceptance of accountability. However, the Naranjo adverse drug reaction probability was used to confirm that the detected cases had at least a probable causal relationship.[10] Bleeding events associated with other drugs, related to trauma or without relevant information for the analysis were excluded. Since edoxaban was introduced in the pharmaceutical provision of the Valencian Health System in July 2016, the follow-up time available for this treatment group in our observation period was much shorter; therefore, edoxaban was excluded in our study.

Data source and study variables

Data were obtained from the corporate electronic information systems: Alumbra (the business intelligence that works on the data warehouse that integrates information of electronic prescriptions), Orion Clinic, Abucasis (the ambulatory medical history) and Farmasyst (the hospital pharmacotherapeutic history). Information about sex, age, main pathology, relevant medical history, laboratory and diagnostic tests, evolution during hospitalisation and ongoing medication (dosage schedules and number of days of treatment) was collected. Electronic dispensing records from the pharmacotherapeutic history were checked to evaluate adherence to medication.

The CHA2DS2-VASc score was used to evaluate the thromboembolic risk.[11] To estimate the bleeding risk we used the HAS-BLED score.[12] The severity of the bleeding events was quantified according to Bleeding Academic Research Consortium (BARC)[13] and International Society on Thrombosis and Haemostasis (ISTH)[14] criteria. The kidney function, expressed by creatinine clearance (CrCl), was estimated by the Cockcroft–Gault method. A follow-up period of 3 months after the hospital discharge was established. A record of the cases was made in a database designed for this purpose using Microsoft Access 2007. This file is subject to safety requirements established by Law 15/1999 and Royal Decree 1720/2007 of personal data protection.

Statistical analyses

Statistical analyses were performed using the statistical package SPSS V.19.0 for Windows. Continuous variables were reported as mean and SD. Relative and absolute frequencies were used for categorical variables. Student t-test and Mann-Whitney U test for independent samples were applied for normally and non-normally distributed data, respectively. The χ^2 test was used to compare proportions.

Incidence rates of the bleeding events, with 95% confidence intervals (CIs), were calculated using the programme Epidat V.3.1: the number of patients with a first hospitalisation episode of bleeding divided by the 100 person-years exposure time at risk. Second or subsequent bleeding events in patients who had several hospitalisations were not included in the calculation.

Ethics

This healthcare quality programme was approved by the Teaching, Investigation and Ethics Commission of Gandia Health Department. Also, it is integrated in research projects managed by the Foundation for the Promotion of Health and Biomedical Research of Valencia (ref. FISABIO 2015/31).

RESULTS

Overall, 37 hospitalisation episodes, in 32 patients, for DOAC-induced bleeding were detected. The study population was distributed according to the drug taken: 15 patients (46.9%) received rivaroxaban, 9 (28.1%) apixaban, and 8 (25.0%) dabigatran. During the study period, one patient with dabigatran and two patients with rivaroxaban each had two hospital admissions, and one patient with dabigatran had three hospital admissions, all of them due to gastrointestinal (GI) bleeds.

Baseline characteristics

Patient baseline characteristics are shown in table 1. Other than DOAC dose, there were no differences in the distribution of these characteristics between treatment groups. The mean (SD) age of the patients was 80.4 (7.9) years and 50.0% were women. The mean (SD) CHA2DS2-VASc and HAS-BLED were 4.5 (1.5) and 2.1 (1.1), respectively. Nine patients (28.1%) had a HAS-BLED ≥3. No patient had severe chronic kidney disease or was on dialysis. Before the DOAC onset, 14 patients (43.8%) were receiving acenocoumarol, three of whom (21.4%) had a prior hospitalisation for bleeding due to treatment with VKA. The average time from DOAC initiation to first hospitalisation episode for bleeding was 501 days (range 2–1365 days).

Bleeding risk factors and indication for dose reduction

On first admission, 19 patients (59.4%) were receiving the DOAC at full dose, four of whom (21.1%) had indication for dose reduction (figure 1A). Considering all hospitalisation episodes, in seven cases (18.9%) there was 'dose reduction indication' and patients were receiving full doses (figure 1B).

Table 2 shows the use of reduced doses of DOACs according to main bleeding risk factors. There were no significant differences in the use of reduced doses between patients with and without these risk factors.

Incidence of bleeding during hospitalisation

Overall, 315 apixaban patients, 301 dabigatran patients and 282 rivaroxaban patients were identified during the study period. Therefore, the included bleeding events represent an incidence rate of 3.44 per 100 person-years (95% CI 2.35 to 4.86) within the 20-month time period, based on a patient´s first hospitalisation for bleeding.

The most common bleeding site was GI (27 cases, 73.0%), representing an incidence rate of 2.37 per 100 person-years (95% CI 1.48 to 3.58). The incidence rate of IC bleeding (three cases, 8.1%) was 0.32 per 100 person-years (95% CI 0.07 to 0.94). Other types of bleeding were muscular haematoma (apixaban, two cases; rivaroxaban, two cases), haemoptysis (dabigatran, one case; rivaroxaban, one case) and haemoperitoneum (apixaban, one case). Major bleeding (MB) occurred in 21 cases (56.8%), representing an incidence rate of 2.15 per 100 person-years (95% CI 1.31 to 3.32) (table 3).

Incidence rates of the hospitalisation episodes according to the DOAC and the type of bleeding are shown in figure 2. No significant differences were found between DOACs, but incidence

Table 1 Baseline demographic and clinical characteristics of the patients according to treatment group

	Apixaban (n=9)	Dabigatran (n=8)	Rivaroxaban (n=15)	All patients (n=32)
Sex, n (%)				
Male	4 (44.4)	5 (62.5)	7 (46.7)	16 (50.0)
Female	5 (55.6)	3 (37.5)	8 (53.3)	16 (50.0)
Age, years				
Mean (SD)	78.2 (6.8)	80.3 (5.1)	81.7 (9.6)	80.4 (7.9)
<65, n (%)	1 (11.1)	–	2 (13.3)	3 (9.4)
65–74, n (%)	–	2 (25.0)	–	2 (6.3)
≥75, n (%)	8 (88.9)	6 (75.0)	13 (86.7)	27 (84.4)
Clinical indication, n (%)				
Paroxysmal NVAF	5 (55.6)	4 (50.0)	8 (53.3)	17 (53.1)
Persistent NVAF	4 (44.4)	4 (50.0)	7 (46.7)	15 (46.9)
Medical history, n (%)				
Congestive heart failure	6 (66.7)	–	7 (46.7)	13 (40.6)
Diabetes	4 (44.4)	1 (12.5)	7 (46.7)	12 (37.5)
Stroke/TIA/thromboembolism	2 (22.2)	1 (12.5)	2 (13.3)	5 (15.6)
Moderate CKD*	2 (22.2)	2 (25.0)	5 (33.3)	9 (28.1)
Vascular disease (PAD, MI)	1 (11.1)	3 (37.5)	4 (26.7)	8 (25.0)
Prior bleeding or predisposition	3 (33.3)	4 (50.0)	6 (40.0)	13 (40.6)
Hypertension	9 (100)	7 (87.5)	13 (86.7)	29 (90.6)
Habitual alcohol consumption	–	–	2 (13.3)	2 (6.3)
CHA2DS2-VASc, mean (SD)	5.0 (1.4)	3.8 (1.0)	4.6 (1.6)	4.5 (1.5)
HAS-BLED				
Mean (SD)	1.9 (0.8)	2.1 (1.0)	2.3 (1.4)	2.1 (1.1)
≥3, n (%)	2 (22.2)	2 (25.0)	5 (33.3)	9 (28.1)
Prior medication use, n (%)				
Aspirin	2 (22.2)	5 (62.5)	8 (53.3)	15 (46.9)
Acenocoumarol	6 (66.7)	3 (37.5)	5 (33.3)	14 (43.8)
Criteria for non-use of VKAs, n (%)				
Allergy or intolerance	–	1 (12.5)	1 (6.7)	2 (6.3)
Poor INR control	5 (55.6)	1 (12.5)	3 (20.0)	9 (28.1)
No access to INR control	3 (33.3)	5 (62.5)	10 (66.6)	18 (56.3)
Previous haemorrhagic stroke	–	1 (12.5)	1 (6.7)	2 (6.3)
Correct INR control but thromboembolic event	1 (11.1)	–	–	1 (3.1)
DOAC dose, n (%)				
Full	8 (88.9)†	2 (25.0)	9 (60.0)	19 (59.4)
Reduced‡	1 (11.1)†	6 (75.0)	6 (40.0)	13 (40.6)
Duration of DOAC§, n (%)				
<3 Months	3 (33.3)	2 (25.0)	3 (20.0)	8 (25.0)
3–12 Months	3 (33.3)	–	4 (26.7)	7 (21.9)
>12 Months	3 (33.3)	6 (75.0)	8 (53.3)	17 (53.1)

*Mean creatinine clearance of 30–49 mL/min for more than 3 months before hospital admission.
†Statistically significant differences (p<0.01) between apixaban and dabigatran groups.
‡A dose <10 mg/day for apixaban, <300 mg/day for dabigatran and <20 mg/day for rivaroxaban.
§Until the first hospital admission for bleeding.
n, number of patients admitted for bleeding.
CKD, chronic kidney disease; DOAC, direct oral anticoagulant; INR, international normalised ratio; MI, myocardial infarction; NVAF, non-valvular atrial fibrillation; PAD, peripheral arterial disease; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

rates of any bleeding event, GI bleeding, MB and type ≥3 BARC bleeding were numerically higher in patients taking rivaroxaban.

Laboratory tests on admission

In 18/37 cases (48.6%), patients presented moderate or severe renal insufficiency, with a mean (SD) serum creatinine of 1.5 (0.3) mg/dL and mean (SD) CrCl of 34.7 (7.2) mL/min. In 2/37 cases (5.4%) patients were admitted with an acute hepatic impairment. The mean (SD) level of serum haemoglobin was 10.8 (3.1) mg/dL, with a mean (SD) decrease of 3.0 (1.9) mg/dL (3.3 (2.0) mg/dL in GI bleedings, 1.1 (1.0) mg/dL in IC bleedings, and 2.6 (1.4) mg/dL in other bleeds). Routine anticoagulant tests were done in all cases (table 3).

Bleeding management and outcomes

Table 4 shows the management and outcomes of the bleeding episodes. In all cases, the DOAC was stopped on admission, and diuresis maintenance and fluid replacement were carried out. In 19 cases (51.4%), patients required blood transfusion (in 17/27 hospitalisations for GI bleeding and in 2/4 hospitalisations for muscular

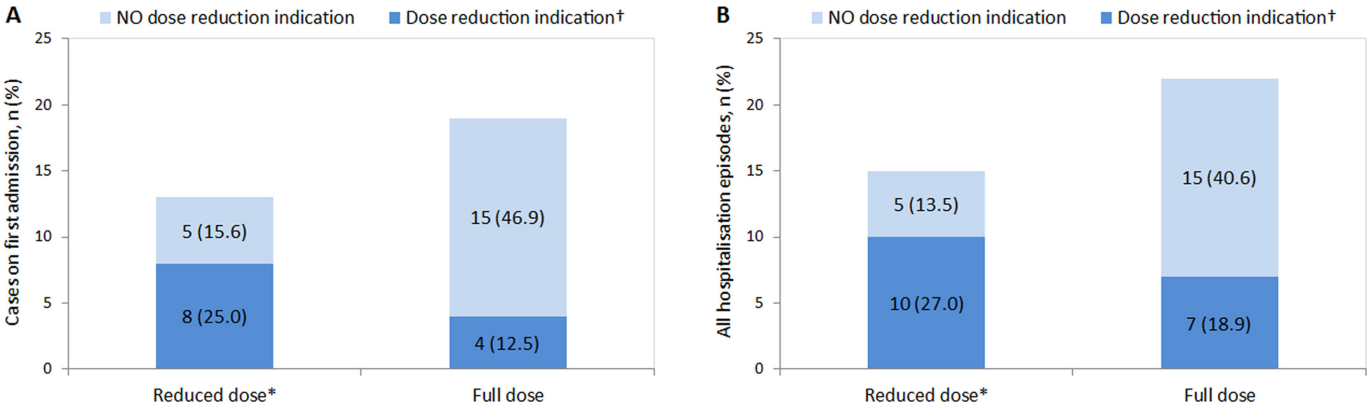

Figure 1 Distribution of detected cases according to the direct oral anticoagulant dose and to the indication (or not) for dose reduction, on first admission (figure 1A) and considering all hospitalisation episodes (figure 1B). *A dose <10 mg/day for apixaban, <300 mg/day for dabigatran and <20 mg/day for rivaroxaban. †For apixaban, patients with severe renal insufficiency (creatinine clearance (CrCl) 15–29 mL/min) or with at least two of the following three criteria: age ≥80 years, body weight ≤60 kg and serum Cr ≥1.5 mg/dL; for dabigatran, age ≥80 years, age 75–79 years with a high bleeding risk, moderate renal insufficiency (CrCl 30–49 mL/min) or treatment with verapamil; and for rivaroxaban, moderate to severe renal insufficiency (CrCl 15–49 mL/min).

haematoma). Three patients (8.1%) died during the hospitalisation: two from the apixaban group (one patient owing to GI bleeding and one patient owing to a respiratory complication) and one patient from the dabigatran group (owing to IC bleeding). At 3 months, overall mortality was 18.8% (6/32 patients).

DISCUSSION

In this study, the real-world safety of DOACs was assessed. We reported an incidence rate of hospitalisation for DOAC-induced bleeding of 3.44 per 100 person-years (95% CI 2.35 to 4.86). In all cases, DOACs were prescribed to prevent thromboembolic complications in patients with non-valvular AF.

Gastrointestinal haemorrhage was the most frequent cause for hospitalisation (27 cases, 73.0%). This observation is consistent with results obtained in the pivotal trials,[2–5] and with previous studies in which emergency and hospital admissions were evaluated in patients who were receiving DOACs.[7–9 15] This increased risk might be related to the low oral bioavailability of DOACs and, therefore, to their direct effect on the GI tract. In patients at high-risk of GI bleeding, VKAs or another DOAC regimen should be preferred over dabigatran 150 mg/12 hours, rivaroxaban 20 mg/24 hours, or edoxabán 60 mg/24 hours.[16] In contrast, IC bleeding was less frequent (three cases, 8.1%), but one of these three patients died during the hospitalisation. This result confirms the severity of this adverse event for patients receiving oral anticoagulant therapy.[15 17–19]

We also analysed the incidence of detected cases according to the DOAC and the type of bleeding. Rivaroxaban was related to non-significant numerically higher incidence rates of any bleeding, GI bleeding, MB, and type ≥3 BARC bleeding. Previously, direct comparisons suggested a higher risk of MB and GI bleeding with rivaroxaban compared with dabigatran,[20–24] and compared with apixaban.[23 24] For IC bleeding, we obtained the same incidence rates for the three drugs. Previous studies reported that the IC bleeding risk was lower with apixaban than with rivaroxaban,[23] but contradictory results have been obtained in direct comparisons between rivaroxaban and dabigatran.[20 22 24] Another study assessed the safety of apixaban, dabigatran and rivaroxaban, comparing each agent with warfarin, and showed that all three DOACs were associated with a lower risk of IC bleeding than warfarin, and only rivaroxaban had an increased risk of GI bleeding.[17]

Previous studies suggested a lower risk of MB and GI bleeding with apixaban than with dabigatran,[23 24] but our data show a similar incidence rate for these two drugs. This may be due to a greater use of the reduced dose of dabigatran (110 mg/12 hours) compared with the reduced dose of apixaban (2.5 mg/12 hours) in the overall population, as observed in the study population. The 150 mg dose of dabigatran was associated with a higher risk of bleeding.[2 19] Differences among patient risk profiles might also explain our results. Thus, as observed in other studies, patients taking dabigatran were younger and had lower risk than patients

Table 2 Use of reduced dose of direct oral anticoagulants (DOACs) with regard to bleeding risk factors in 32 patients admitted for DOAC-induced bleeding

Risk factor	Patients, n (%)	Reduced dose*, n (%)	p Value
HAS-BLED score			
≥3	9 (28.1)	4 (44.4)	0.783
0–2	23 (71.9)	9 (39.1)	
Age			
≥80 years	23 (71.9)	11 (47.8)	0.184
<80 years	9 (28.1)	2 (22.2)	
Hypertension			
Yes	29 (90.6)	13 (44.8)	0.132
No	3 (9.4)	–	
Concomitant medication†			
Yes	17 (53.1)	9 (52.9)	0.131
No	15 (46.9)	4 (26.7)	
History‡			
Yes	13 (40.6)	7 (53.8)	0.208
No	19 (59.4)	6 (31.6)	
Moderate chronic kidney disease§			
Yes	9 (28.1)	5 (55.6)	0.282
No	23 (71.9)	8 (34.8)	

*A dose <10 mg/day for apixaban. <300 mg/day for dabigatran and <20 mg/day for rivaroxaban.
†Concomitant use of antiplatelet agents, non-steroidal anti-inflammatory drugs or P-glycoprotein inhibitors (eg, verapamil, diltiazem, amiodarone and dronedarone).
‡ Personal medical history of bleeding and/or predisposition (anaemia, coagulation disorders, chronic gastritis, etc).
§Mean creatinine clearance of 30-49 mL/min for more than 3 months before hospital admission.

Table 3 Clinical characteristics of the patients on admission according to treatment group

	Apixaban (n=9)	Dabigatran (n=11)	Rivaroxaban (n=17)	All hospitalisations (n=37)
Bleeding site, n (%)				
Gastrointestinal	5 (55.6)	9 (81.8)	13 (76.5)	27 (73.0)
Intracranial	1 (11.1)	1 (9.1)	1 (5.9)	3 (8.1)
Other location	3 (33.3)	1 (9.1)	3 (17.6)	7 (18.9)
Bleeding severity, n (%)				
Major bleeding*	5 (55.6)	5 (45.5)	11 (64.7)	21 (56.8)
Fatal bleeding*	1 (11.1)	1 (9.1)	–	2 (5.4)
Type 2 BARC bleeding	4 (44.4)	5 (45.5)	4 (23.5)	13 (35.1)
Type ≥3 BARC bleeding	5 (55.6)	6 (54.5)	13 (76.5)	24 (64.9)
Hepatic dysfunction†, n (%)	–	–	2 (11.8)	2 (5.4)
Hb, mean (SD), mg/dL	11.5 (2.4)	11.6 (3.4)	10.0 (3.1)	10.8 (3.1)
Decrease in Hb, mean (SD), mg/dL	3.2 (2.0)	2.4 (1.3)	3.3 (2.2)	3.0 (1.9)
RBC count, mean (SD), x10^9/L	4.1 (0.6)	5.2 (2.8)	3.6 (0.9)	4.2 (1.8)
Serum Cr, mean (SD), mg/dL	1.4 (0.4)	0.9 (0.4)	1.3 (0.5)	1.2 (0.5)
CrCl, mL/min				
Mean (SD)	48.3 (25.5)	82.5 (28.8)	47.6 (19.7)	58.1 (28.4)
≥50, n (%)	3 (33.3)	9 (81.8)	7 (41.2)	19 (51.4)
30–49, n (%)	4 (44.5)	2 (18.2)	6 (35.3)	12 (32.4)
15–29, n (%)	2 (22.2)	–	4 (23.5)	6 (16.2)
Coagulation test, mean (SD)				
INR	1.6 (0.4)	1.4 (0.2)	1.5 (0.5)	1.5 (0.4)
PT, s	18.8 (3.9)	16.8 (2.1)	18.4 (4.3)	18.0 (3.7)
QI, %	56.0 (14.0)	66.0 (14.0)	60.7 (19.8)	61.1 (16.9)
aPTT, s	36.8 (7.7)	46.3 (12.9)	33.6 (4.6)	38.4 (10.1)
Medication use, n (%)				
Antiplatelets	–	7 (63.6)	5 (29.4)	12 (32.4)
NSAIDs	–	3 (27.3)	3 (17.6)	6 (16.2)
Amiodarone	3 (33.3)	3 (27.3)	4 (23.5)	10 (27.0)
Dronedarone	–	–	1 (5.9)	1 (2.7)
Diltiazem	–	3 (27.3)	3 (17.6)	6 (16.2)
Verapamil	–	–	1 (5.9)	1 (2.7)
Proton pump inhibitors	5 (55.6)	9 (81.8)	15 (88.2)	29 (78.4)

*According the International Society on Thrombosis and Haemostasis bleeding scale.
†Bilirubin >2 times the upper normal limit and aspartate/alanine aminotransferase >3 times the upper normal limit.
n, number of hospitalisation episodes for bleeding.
aPTT, activated partial thromboplastin time; BARC, Bleeding Academic Research Consortium; Cr, creatinine; CrCl, creatinine clearance; Hb, haemoglobin; INR, international normalised ratio; NSAIDs, non-steroidal anti-inflammatory drugs; PT, prothrombin time; QI, Quick index; RBC, red blood cell.

receiving apixaban and rivaroxaban.[17] Therefore, it is necessary to analyse the baseline characteristics of the overall population who are receiving treatment with apixaban, dabigatran and rivaroxaban, and not only those of the patients who have been admitted, in order to establish if there are differences in the bleeding risks between DOACs.

The bleeding risk may be greater during the first 120 days of exposure to DOACs.[23] In 25.0% of our patients, the first hospital admission occurred within the first 3 months after DOAC initiation. This result reinforces the need for an ongoing review of treatment, preferably after 1 month initially, and later every 3 months.[25] Also, bleeding risk factors, such as advanced age (≥75–80 years), renal insufficiency and concomitant medication, play a key role in the choice of the type and dose of DOAC.[16 25] The mean age of our patients was 80.4 years, and 71.9% of them were aged ≥80 years. Recently, it has been observed that apixaban appears to have the lowest risk of GI bleeding for patients aged >75 years.[23] Our results point to this observation, because the reported incidence rate of GI bleeding in patients receiving apixaban was numerically the lowest. The kidney function, which is directly related to age, must be taken into account when a DOAC is prescribed and it should be evaluated at least yearly, and in the elderly at least once every 6 months.[25] In 48.6% of the hospitalisations, patients were admitted with moderate to severe renal insufficiency (CrCl 15–49 mL/min), and 28.1% of them had moderate chronic kidney disease (CrCl 30–49 mL/min). In these patients, DOAC adjustment to reduced doses is recommended, but it must be noted that dabigatran is not approved in Europe for use in patients with CrCl <30 mL/min, and all DOACs are contraindicated when the CrCl is <15 mL/min.[16 25 26] Additionally, drugs like P-glycoprotein inhibitors (eg, verapamil, diltiazem, amiodarone and dronedarone), antiplatelets and non-steroidal anti-inflammatory drugs, in combination with DOACs, may result in pharmacokinetic and pharmacodynamic interactions.[25] Of our patients, 53.1% were concomitantly taking some of these drugs, resulting in a potentially increased bleeding risk.

Although the previous risk factors were considerably prevalent in our patients, none were individually associated with the use of reduced doses of DOACs. This can be explained by the heterogeneity in the dose adjustment criteria among DOACs and because in certain cases dose reduction should be considered if two or more risk factors are present. In other studies, some bleeding

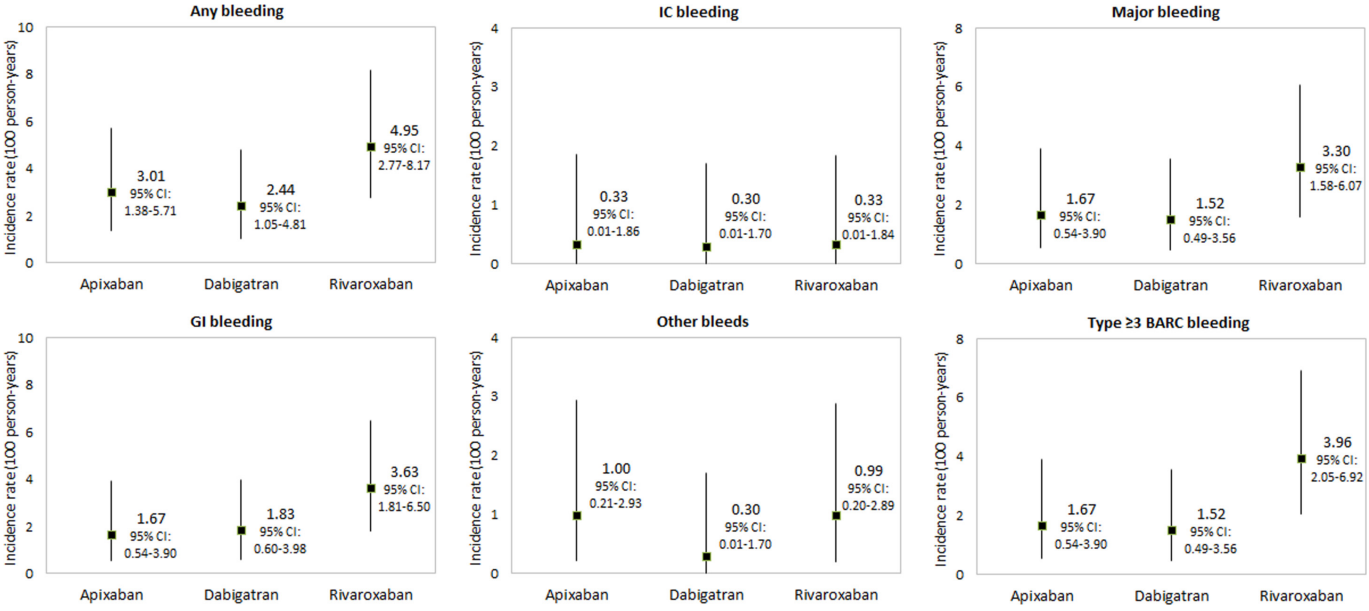

Figure 2 Incidence rates (per 100 person-years) of the hospitalisation episodes according to the direct oral anticoagulant and the type of bleeding. The vertical bars correspond to the 95% confidence intervals (CIs). BARC, Bleeding Academic Research Consortium; GI, gastrointestinal; IC, intracranial.

risk factors were independent predictors for using the lower or higher doses of DOACs.[27] Considering jointly the recommendations in clinical guidelines for DOAC dose adjustment,[16 25 26] on first admission, four patients (12.5%) were receiving full doses and had ´dose reduction indication´. Overdose and, therefore, overexposure to DOACs may be directly related to the development of a bleeding event in these patients. Similarly, five patients (15.6%) were taking the DOAC at a reduced dose and had no ´dose reduction indication´. These low doses of anticoagulants were prescribed for patients who did have other risk factors, such as hypertension or history of bleeding. Therefore, healthcare quality programmes should focus on whether patients are receiving the correct dose according to the available evidence.

Table 4 Clinical management and outcomes of the bleeding episodes

	All hospitalisations (n=37)
Pharmacological therapy, n (%)	
Intravenous iron	13 (35.1)
Vitamin K	8 (21.6)
Desmopressin	5 (13.5)
Prothrombin complex concentrate*	4 (10.8)
Tranexamic acid	2 (5.4)
Idarucizumab	2† (5.4)
Blood transfusion, n (%)	
1 Unit	1 (2.7)
2–3 Units	14 (37.8)
4–5 Units	4 (10.8)
Endoscopic haemostatic procedure‡, n (%)	2 (5.4)
Transferred to intensive care unit, n (%)	1 (2.7)
Length of hospitalisation, mean (SD), days	8.4 (5.2)
Hospitalisation outcome, n (%)	
Discharged	31 (83.8)
Transferred to long-stay hospital	3 (8.1)
Died	3 (8.1)
DOAC treatment decision in survivors, n (%)	
Definitively stopped	14 (37.8)
Continued	14 (37.8)
Dose reduction	4 (10.8)
Switched for other DOAC	2 (5.4)

*Blood coagulation factors IX, II, VII and X in combination.
†In 2/11 (18.2%) hospital admissions in the dabigatran group.
‡Argon plasma coagulation or/and endoscopic haemoclip placement.

Our results show that haemorrhagic emergency complications can be effectively managed simply by providing supportive therapy and withholding the DOAC temporarily, and the DOAC effect does not need to be actively reversed in most patients.[28] After DOAC cessation, restoration of haemostasis is to be expected within 12–24 hours after the last dose taken,[25] but factors such as kidney dysfunction and/or concomitant use of antiplatelet agents, non-steroidal anti-inflammatory drugs or P-glycoprotein inhibitors, can complicate the DOAC clearance and the haemostasis recovery. Therefore, non-specific (eg, blood transfusion, tranexamic acid, desmopressin and prothrombin complex concentrates) and specific reversal treatments may be necessary.[25 26 28] Nowadays, idarucizumab, which binds dabigatran with high affinity, is the only marketed specific anti-DOAC. In eight hospitalisations (21.6%), vitamin K was used, but this traditional antidote is ineffective for reversing the DOAC activity.[28] Moreover, assessment of exposure to DOACs by coagulation assays may be needed in these situations. Most of our patients presented abnormal coagulation parameters on admission, but the coagulation tests currently used in our hospital are not very sensitive and give only an approximate assessment of the effects of DOACs on coagulation. Other tests, like ecarin clotting time, diluted thrombin time or clot-based factor Xa assays, offer a quantifiable dose–response.[28] Once the patient´s clinical condition is stabilised, restarting the DOAC should balance the risk of thromboembolism against the bleeding risk. In 14 cases (37.8%), the DOAC was definitively stopped after hospital discharge. Physician experience and patient preferences were considered in this decision.

Our study has four main limitations. First, this was an observational study and may be subject to residual confounding and unmeasured factors. Second, the included cases have been identified on the basis of information and encoded data in healthcare

reports, which might have had omissions of information and errors in coding. Third, the sample size was small, so the results obtained and the conclusions reached must be interpreted cautiously. Fourth, our study did not include edoxaban, which was approved in July 2016, because the follow-up period would not have been insufficiently long to compare its safety with those of other DOACs.

All included cases in this study were reported to the Spanish Pharmacovigilance System for medicinal products for human use.

CONCLUSIONS

DOACs are associated with serious bleeding events that require hospitalisation. Gastrointestinal bleeding was prominent among the hospital admissions, while intracranial bleeding was rare. In detected cases, a high prevalence of bleeding risk factors existed. Also, a non-negligible number of patients received DOACs at inappropriate doses based on individual (patient-specific) characteristics and according to clinical recommendations. A careful pharmacotherapeutic follow-up and individualised risk/benefit ratio assessment, especially in patients who are elderly, polymedicated or have impaired renal function, can serve as a basis on which to reinforce the safe use of DOACs.

What this paper adds

What is already known on this subject?

- Since market authorisation of direct oral anticoagulants (DOACs), their use in clinical practice is increasing rapidly.
- DOACs are suitable alternatives to vitamin K antagonists for prevention of thromboembolic complications, such as stroke, in patients with non-valvular atrial fibrillation.
- The therapeutic effects of DOACs have been associated with a risk for developing haemorrhagic events, such as gastrointestinal and intracranial bleeding.

What this study adds?

- Bleeding risk factors were considerably prevalent in detected hospital admissions, but none were individually associated with the use of reduced doses of DOACs.
- The non-negligible percentage of detected cases who received full doses of DOACs and had a ´dose reduction indication' can serve as a basis on which to evaluate the need to implement corrective measures to reinforce the safe use of DOACs.

Competing interests None declared.

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Hospital admissions for bleeding events associated with treatment with apixaban, dabigatran and rivaroxaban

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