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Risk of bleeding in hospitalized patients on anticoagulant therapy: Prevalence and potential risk factors

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ABSTRACT

Introduction: Bleeding is the most important complication of treatment with anticoagulant therapy. Although several studies have identified risk factors of bleeding in outpatients, no studies have been performed that evaluated prevalence and potential risk factors of bleeding in hospitalized patients treated with anticoagulant therapy.

Methods: The primary objective of this study was to determine the prevalence of bleeding in anticoagulant users during hospitalization. The secondary objective was to identify potential risk factors of bleeding in hospitalized patients on anticoagulant therapy.

A prospective, observational cohort study was conducted in two Dutch hospitals. Adult patients hospitalized between October 2015 and October 2016 treated with anticoagulant therapy were included. Bleeding was defined as a composite endpoint of major bleeding and non-major bleeding according to the International Society on Thrombosis and Heamostasis (ISTH) criteria. Data analysis was performed by multivariate logistic regression.

Results: The prevalence of in-hospital bleeding in patients using anticoagulant therapy was 7.2%; 95% confidence interval [95% CI] 5.5–9.1 (65 out of 906 patients). Multivariate logistic regression analysis indicated that female gender (adjusted odds ratio [ORadj] 2.1; 95% CI 1.2–3.7), high-bleeding-risk surgical procedure (ORadj 5.3; 95% CI 2.7–10.2), low-bleeding-risk surgical procedure (ORadj 4.9; 95% CI 1.9–12.6), and non-surgical interventions (ORadj 6.2; 95% CI 3.0–12.6) were associated with bleeding events in hospitalized patients treated with anticoagulants.

Conclusions: The prevalence of bleeding in anticoagulant users during hospitalization was 7.2%. This study detected potential risk factors that can help to identify patients on anticoagulants who have an increased risk of bleeding during hospitalization.

1. Introduction

Anticoagulants are frequently used medications in the prevention and treatment of thromboembolic disease [1,2]. Despite the clinical benefits, bleeding is the most important complication of treatment with anticoagulants [1,3]. In the Netherlands, the HARM (Hospital Admissions Related to Medication) study showed that 5.6% of all unplanned hospitalizations were drug-related and that 6.3% of these drug-related hospitalizations were attributable to the use of anticoagulants and 8.7% to antiplatelet drugs [4].

Various studies have identified risk factors of bleeding in patients treated with anticoagulants. Shoeb et al. and Fitzmaurice et al. reported that increasing age and female gender are associated with increased risk of bleeding [5,6]. Other risk factors of bleeding were comorbidities (such as cancer, hypertension, diabetes, renal impairment, anemia, bleeding in history, and genetic polymorphism) and concomitant use of interacting drugs [7–12].

Most published studies focused on risk factors of bleeding in outpatients treated with vitamin K antagonists (VKAs) for specific indications, such as atrial fibrillation (AF) or venous thromboembolism (VTE) [7–11]. However, little is known about the potential risk factors of bleeding in hospitalized patients treated with anticoagulants. Compared to outpatients, hospitalized patients may be at increased risk of bleeding, for example because of perioperative bridging of

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anticoagulation therapy and start of additional medication influencing the metabolism of anticoagulants [13,14]. Furthermore, most studies identified risk factors of bleeding in patients treated with VKAs and did not include patients using direct oral anticoagulants (DOACs) [7–11].

The primary aim of this study was to determine the prevalence of bleeding in anticoagulant users during hospitalization. Secondary goal was to identify potential risk factors of bleeding in hospitalized patients treated with anticoagulant therapy.

2. Methods

2.1. Study design

The design of this study is a prospective, observational multicenter cohort study. This study is part of a larger antithrombotic stewardship study (S-team study), in which the effect of a multidisciplinary antithrombotic team on the safety and efficacy regarding antithrombotic therapy during hospitalization is studied using a pre-post study design [15]. We aim to include 1900 patients, 950 patients in the pre-implementation phase and 950 patients in the post-implementation phase of the S-team study. For this study all patients from the pre-implementation phase of the S-team study were enrolled. The S-team study was approved by the Medical Ethics Committee of the Erasmus University Medical Center (MEC-2015-386).

2.2. Study setting

The study is conducted in the Erasmus University Medical Center (EMC) and the Reinier de Graaf Hospital (RdGG). The EMC is a 1320-bed University Medical Center based in Rotterdam, the Netherlands. The RdGG is a general teaching hospital located in Delft, the Netherlands, with 590 beds.

2.3. Study population

Patients aged 18 years and older who were admitted to the EMC and RdGG between October 2015 and October 2016 and treated with anticoagulant therapy were eligible for inclusion. The study population consisted of patients who started with anticoagulant therapy in the hospital, patients who were already treated with anticoagulant therapy before hospitalization and patients who restarted anticoagulant therapy after a surgical or non-surgical intervention. Owing to the limited availability of study personnel, we recruited three patients per day per hospital. A random number generator was used to select those three patients. Only the patient's first hospital admission was included. All participants provided informed consent during hospitalization. Exclusion criteria were the following: (1) no informed consent from the patient, (2) hospitalization for < 24 h, (3) admission to the intensive care unit (ICU) without admission to a general care ward, (4) patients treated with low-molecular-weight-heparins (LMWHs) only as thrombosis prophylaxis, (5) patients started with acenocoumarol three days or less, phenprocoumon five days or less, or DOACs one day or less prior to hospital discharge were excluded for analysis.

2.4. Data collection

The hospital information system was used for data collection (Table S1). Patient data were coded according to Dutch privacy guidelines. Data were collected during hospital stay from the day of hospitalization or time of establishing the first anticoagulant therapy or from the day of discharge of the ICU to a general care ward until discharge from hospital or patient death. In patients who were initially admitted to a general care ward and subsequently transferred to the ICU, data were collected from the day of hospitalization until admission to the ICU.

2.4.1. Potential risk factors

The following potential risk factors, based on identified risk factors of bleeding in outpatients, were included in the analysis: gender, age, bleeding in history (yes/no), cancer (yes/no), hospital type (University Medical Center vs general teaching hospital), bleeding risk of the surgical procedure (high, low, and clinically non-relevant bleeding risk) [17,18], non-surgical interventions (endoscopic interventions and endovascular coiling) (yes/no), estimated glomerular filtration rate (e-GFR) on the day of hospitalization, type of anticoagulant therapy and concomitant use of known interacting drugs.

We defined concomitant use of known interacting drugs as an active prescription at the same time the VKA or DOAC was prescribed. The following drugs were considered as interacting drugs that increase the effect of VKAs the most; miconazole, cotrimoxazole, fluconazole, voriconazole and amiodarone [19]. Ketoconazole, itraconazole, voriconazole, cyclosporine, tacrolimus and verapamil were considered to increase the effect of DOACs the most [19]. The interacting drugs with VKAs and DOACs were clustered for the analysis into two groups; VKA interacting drugs and DOAC interacting drugs.

2.5. Outcome

Primary outcome was the prevalence of bleeding in anticoagulant users during hospitalization. Patients with bleeding as a reason for admission were also eligible for inclusion; however those bleeding events were not included in the primary endpoint. Bleeding was defined as a composite endpoint of major bleeding and non-major bleeding according to the International Society on Thrombosis and Heamostasis (ISTH) criteria (Table 1) [20,21]. Because our study started in 2015 we did not use the most recent ISTH classification of bleeding. The bleeding events were evaluated and classified according to the ISTH criteria by two independent expert physicians in the field (FNC and EK). In patients where more than one bleeding event was observed during hospitalization, only the first bleeding event was included.

Secondary outcome was the potential risk factors that are associated with bleeding in hospitalized patients on anticoagulant therapy.

2.6. Sample size

Annual bleeding (major and non-major) rates are 2–3% depending on the type of anticoagulant, but in every day practice it seems that this rate is at least 10% [22–24]. Based on the number of potential risk factors included in the analysis (nine potential risk factors) and the assumption that ten cases are needed for every predictor studied [25], the required sample size will be 900 patients. In order to account for drop-outs, 950 patients will be included.

2.7. Data analysis

All data were processed with Open Clinica® and analyzed with SPSS version 21.0. Descriptive statistics were used to determine the prevalence of bleeding in anticoagulant users during hospitalization. Univariate logistic regression analysis was performed to identify potential risk factors of bleeding during hospitalization. Potential risk factors that showed a significant association ($p < .1$) in the univariate analysis were entered in a multivariate model, using a stepwise enter method. Variables that changed the beta-coefficient with > 10% were retained in the model. Adjusted odds ratio's (ORadj) and 95% confidence intervals (95% CI) were reported.

We planned to perform a sensitivity analysis for the potential risk factor, VKA interacting drugs, including only patients who used VKAs.

Table 1
ISTH definitions of bleeding in patients.

Type of bleeding	Definition of bleeding
Major bleeding in non-surgical patients [Schulman 2005]	1. Fatal bleeding, and/or 2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or 3. Bleeding causing a fall in hemoglobin level of 20 g/l (1.24 mmol/l)
Major bleeding in surgical patients [Schulman 2010]	1. Fatal bleeding, and/or 2. Bleeding that is symptomatic and occurs in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, in a non-operated joint, or intramuscular with compartment syndrome, assessed in consultation with the surgeon, and/or 3. Extrasurgical site bleeding causing a fall in hemoglobin level of 20 g/l (1.24 mmol/l) or more, or leading to transfusion of two or more units of whole blood or red cells, with temporal association within 24–48 h to the bleeding, and/or 4. Surgical site bleeding that requires a second intervention (open arthroscopic, endovascular) or a haemarthrosis of sufficient size as to interfere with rehabilitation by delaying mobilisation or delayed wound healing, resulting in prolonged hospitalization or a deep wound infection, and/or 5. Surgical site bleeding that is unexpected and prolonged and/or sufficiently large to cause haemodynamic instability, as assessed by the surgeon. There should be an associate fall in hemoglobin level of at least 20 g/l (1.24 mmol/l), or transfusion, indicated by the bleeding, of at least two units of whole blood or red cells, with temporal association within 24 h to the bleeding.
Non-major bleeding	All bleeding events that do not meet the ISTH criteria according to which major bleeding is defined.

ISTH, International Society of Thrombosis and Haemostasis.

3. Results

3.1. Study population

During the study period 1384 patients were eligible for inclusion. In 469 patients, at least one reason for exclusion was present. Nine patients withdrew their consent after signing the informed consent. In total 906 patients were included in our analysis (Fig. 1). Characteristics of the included patients are presented in Table 2. Of these, 544 (60%) were male, median age was 70 (range 59–78) years and 323 (35.7%) patients had surgery. The most frequently performed surgical procedures were cardio-thoracic (27.2%), vascular (24.5%) and trauma and orthopedic (13.9%). Admission for medical reasons occurred in 583 (64.3%) patients. We included 365 (40.3%) patients who were admitted through the emergency department. Median length of stay in all patients was 8 days with a range of 5 to 14 days. The median length of stay in patients with a bleeding during hospitalization was 18 days (range of 8.5 to 34.5 days), and 7 days (range of 4 to 13 days) in patients without a bleeding during hospitalization.

The most frequently used anticoagulants were VKA monotherapy (31.9%) and simultaneous use of VKA and LMWH because of perioperative bridging therapy (21.6%). Of the 668 VKA and DOAC users in our study, 75 (11.2%) patients were prescribed a VKA or DOAC for the first time.

Combination of anti-platelet therapy with VKAs or DOACs occurred in 158 patients. Detailed information on type and dose of the received

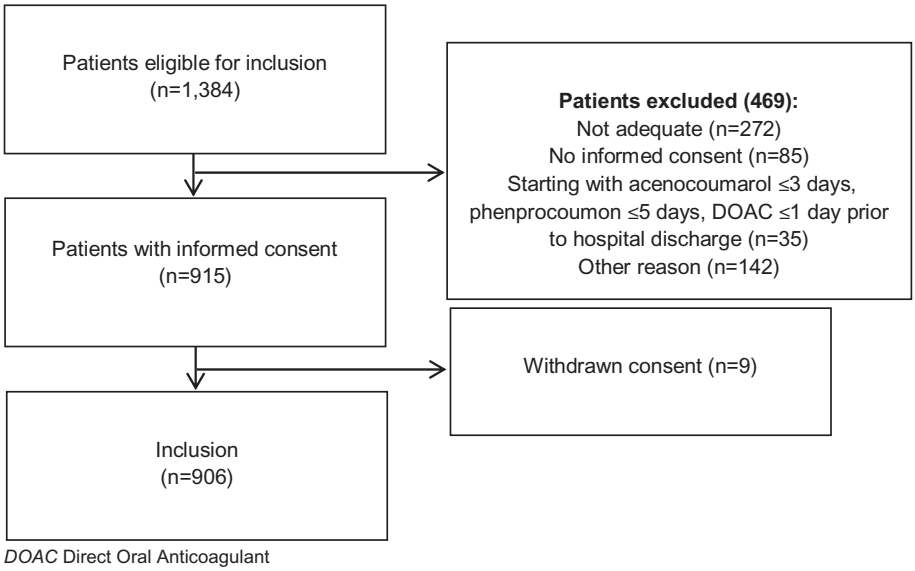

Fig. 1. Study flow.
DOAC Direct Oral Anticoagulant.

Table 2
Baseline characteristics of the patients.

Characteristic	All patients (n = 906)	Patients with bleeding during hospitalization (n = 65)	Patients without bleeding during hospitalization (n = 841)
Male gender	544 (60)	31 (47.7)	513 (61)
Age, years	70 [59–78]	70 [57.5–79]	70 [59–78]
Length of hospitalization, days	8 [5–14]	18 [8.5–34.5]	7 [4–13]
Prior bleeding	194 (21.4)	11 (16.9)	183 (21.8)
Thrombocytopenia	8 (0.9)	2 (3.1)	6 (0.7)
Cancer	221 (24.4)	18 (27.7)	203 (24.1)
Hospital type, University Medical Center	454 (50.1)	45 (69.2)	409 (48.6)
Surgery			
High bleeding risk procedure	227 (25.1)	34 (52.3)	193 (22.9)
Low bleeding risk procedure	57 (6.3)	8 (12.3)	49 (5.8)
Clinically non-relevant bleeding risk procedure	39 (4.3)	3 (4.6)	36 (4.3)
Non-surgical interventions	80 (8.8)	16 (24.6)	64 (7.6)
e-GFR, $\leq$50 ml/min/1.73m^2	293 (32.3)	21 (32.3)	272 (32.3)
Type of anticoagulant therapy			
VKA monotherapy	289 (31.9)	11 (16.9)	278 (33.1)
DOAC monotherapy	54 (6.0)	3 (4.6)	51 (6.1)
LMWH monotherapy	139 (15.3)	14 (21.5)	125 (14.9)
VKA + LMWH	196 (21.6)	19 (29.2)	177 (21.0)
Combination of SAPT with a VKA or DOAC or LMWH	144 (15.9)	14 (21.5)	130 (15.5)
Combination of DAPT with a VKA or DOAC or LMWH	84 (9.3)	4 (6.2)	80 (9.5)
VKA interacting drugs	124 (13.7)	12 (18.5)	112 (13.3)

Results are presented as median [interquartile range] or as number of patients (%) for non-continues data. N, number of patients at risk; e-GFR, estimated glomerular filtration rate calculated with the modification of diet in renal disease (MDRD) formula [16]; VKA, vitamin-K antagonist; DOAC, direct oral anticoagulant; LMWH, low-molecular-weight-heparin; SAPT, single antiplatelet therapy; DAPT, dual antiplatelet therapy.

Table 3
Type and dose of antiplatelet drug in addition to treatment with VKAs or DOACs.

Type and dose of antiplatelet drug in combination with a VKA or DOAC	All users (n = 158)
Combination of a VKA with SAPT	125 (79.1)
Acetylsalicylic acid 80 mg once daily	50 (31.6)
Calcium carbasalate 100 mg once daily	17 (10.8)
Clopidogrel 75 mg once daily	55 (34.8)
Prasugrel 5 mg once daily	1 (0.6)
Ticagrelor 90 mg twice daily	2 (1.3)
Combination of a VKA with DAPT	23 (14.6)
Acetylsalicylic acid 80 mg once daily + Clopidogrel 75 mg once daily	10 (6.3)
Calcium carbasalate 100 mg once daily + Clopidogrel 75 mg once daily	5 (3.2)
Calcium carbasalate 100 mg once daily + Ticagrelor 90 mg twice daily	8 (5.1)
Combination a DOAC with SAPT	8 (5.1)
Dabigatran 110 mg twice daily + Acetylsalicylic acid 80 mg once daily	1 (0.6)
Dabigatran 110 mg twice daily + Calcium carbasalate 100 mg once daily	3 (1.9)
Dabigatran 110 mg twice daily + Clopidogrel 75 mg once daily	3 (1.9)
Rivaroxaban 15 mg once daily + Acetylsalicylic acid 80 mg once daily	1 (0.6)
Combination of a DOAC with DAPT	2 (1.2)
Apixaban 5 mg twice daily + Calcium carbasalate 100 mg once daily + Clopidogrel 75 mg once daily	1 (0.6)
Dabigatran 110 mg twice daily + Calcium carbasalate 100 mg once daily + Clopidogrel 75 mg once daily	1 (0.6)

N, number of patients at risk; VKA, vitamin-K antagonist; DOAC, direct oral anticoagulant; SAPT, single antiplatelet therapy; DAPT, dual antiplatelet therapy.

antiplatelet drugs are listed in Table 3.

The majority of enrolled patients received anticoagulant therapy for the treatment of venous thromboembolism (48.2%), atrial fibrillation (42.9%), cardiac valve surgery (3.2%) and other reasons (5.7%). VKA interacting drugs were used in 124 (13.7%) patients. Due to the low number of DOAC users during our study period we found no concomitant use of interacting drugs with DOACs.

3.2. Characteristics of all bleeding events

The prevalence of all in-hospital bleeding in patients using anticoagulant therapy was 7.2%; 95% CI 5.5–9.1 (65 out of 906 patients). Seven patients had two bleeding events during hospitalization and in two patients three bleeding events occurred during hospitalization. Two patients that were admitted because of a bleeding developed a new bleeding event during hospitalization.

Of the 65 patients with a bleeding, 51 (78.5%) were categorized as major bleeding and 14 (21.5%) as non-major bleeding.

The most common sites of bleeding were surgical site bleeding (n = 47, 72.3%), followed by gastrointestinal bleeding (n = 9, 13.8%) and urogenital bleeding (n = 4, 6.1%). One out of seventy seven endoscopic interventions was complicated by bleeding. Of the 65 bleeding events, one contributed to death, 48 were associated with a fall in hemoglobin level of $\geq$20 g/l (1.24 mmol/l), and 39 led to a transfusion of two or more units of whole blood or red cells. In 44 patients on VKA therapy, four patients had an International normalized ratio (INR) of > 3.5 at the time of bleeding. Five patients had an INR between 2 and 3, and an INR of < 2 was noticed in 32 patients at the time of bleeding. In three patients the INR was unknown. Four patients were treated with DOACs at the time of bleeding. The DOACs were correctly dosed in all four patients.

3.2.1. Bleeding in non-surgical patients

The prevalence of in-hospital bleeding in non-surgical patients using anticoagulant therapy was 2.2% (13 out of 583 patients); 7 (53.8%) patients with major and 6 (46.2%) patients with non-major bleeding. The most common sites of bleeding were gastrointestinal bleeding ($n = 5$, 38.5%) and urogenital bleeding ($n = 4$, 30.8%). Of the 13 bleeding events, 7 were associated with a fall in hemoglobin level of ≥ 20 g/l (1.24 mmol/l), and 5 led to a transfusion of two or more units of whole blood or red cells.

3.2.2. Bleeding in surgical patients

In-hospital bleeding occurred in 52 out of 323 (16.1%) surgical patients. All patients with surgical-associated bleeding were on active anticoagulation when the bleeding occurred. Major bleeding occurred in 44 (84.6%) patients, non-major bleeding in 8 (15.4%) patients. Surgical site bleeding was the most frequent site of bleeding ($n = 47$, 90.4%). Forty-one bleeding events were associated with a fall in hemoglobin level of ≥ 20 g/l (1.24 mmol/l), and 34 led to a transfusion of two or more units of whole blood or red cells.

3.3. Potential risk factors of bleeding

Details of the univariate and multivariate logistic regression analysis to identify potential risk factors of any bleeding in hospitalized patients treated with anticoagulants are presented in Table 4. After multivariate analysis, the following variables were identified as predictors for any bleeding: female gender (ORadj 2.1; 95% CI 1.2–3.7), high-bleeding-risk surgical procedure (ORadj 5.3; 95% CI 2.7–10.2), low-bleeding-risk surgical procedure (ORadj 4.9; 95% CI 1.9–12.6), and non-surgical interventions (ORadj 6.2; 95% CI 3.0–12.6). The sensitivity analysis for the VKA interacting drugs predictor, including only patients who have used VKAs, showed no increased risk of bleeding in the multivariate analysis. Stratified analysis for major bleeding events showed similar predictors (Table S2).

Table 4
Potential risk factors of any bleeding in hospitalized patients on anticoagulant therapies after univariate logistic regression (odds ratio) and multivariate logistic regression (adjusted odds ratio).

Potential determinant	OR [95% CI]	ORadj [95% CI]
Female gender	**1.7 [1.0–2.8]**	**2.1 [1.2–3.7]**
Age, years	1.0 [1.0–1.0]	–
Bleeding in history	0.7 [0.4–1.4]	–
Cancer	1.2 [0.7–2.1]	–
Hospital type		
General teaching hospital	Ref.	
University Medical Center	**2.4 [1.4–4.1]**	1.3 [0.7–2.4]
Surgery		
No surgery	Ref.	
High bleeding risk procedure	**4.9 [2.8–8.8]**	**5.3 [2.7–10.2]**
Low bleeding risk procedure	**4.6 [1.9–11.0]**	**4.9 [1.9–12.6]**
Clinically non-relevant bleeding risk procedure	**2.3 [0.7–8.3]**	1.9 [0.5–7.0]
Interventions		
No non-surgical interventions	Ref.	
Non-surgical interventions	**4.0 [2.1–7.4]**	**6.2 [3.0–12.6]**
e-GFR		
> 50 ml/min/1.73 m2	Ref.	
≤ 50 ml/min/1.73 m2	1.0 [0.6–1.7]	–
Type of anticoagulant therapy		
VKA monotherapy	Ref.	
DOAC monotherapy	1.5 [0.4–5.5]	–
LMWH monotherapy	**2.8 [1.3–6.4]**	2.0 [0.8–5.0]
VKA + LMWH	**2.7 [1.3–5.8]**	1.8 [0.8–4.1]
Combination of SAPT with a VKA or DOAC or LMWH	**2.7 [1.2–6.3]**	2.1 [0.9–4.9]
Combination of DAPT with a VKA or DOAC or LMWH	1.3 [0.4–4.1]	–
Interacting drugs		
No VKA interacting drugs	Ref.	
VKA interacting drugs	1.5 [0.8–2.8]	–
Sensitivity analysis VKA interacting drugs	**1.9 [1.0–3.6]**	1.5 [0.7–3.2]

Numbers in bold are statistically significant. OR, odds ratio; 95%CI, 95% confidence interval; ORadj, adjusted odds ratio; e-GFR, estimated glomerular filtration rate calculated with the modification of diet in renal disease (MDRD) formula [16]; VKA, vitamin-K antagonist; DOAC, direct oral anticoagulant; LMWH, low-molecular-weight-heparin; SAPT, single antiplatelet therapy; DAPT, dual antiplatelet therapy.

4. Discussion

In our study, we found that the prevalence of in-hospital bleeding events in patients using anticoagulant therapy was 7.2%; 95% CI 5.5–9.1 in all patients (65 out of 906 patients), and as high as 16.1% in surgical patients. Of all bleeding events, 78.5% were major bleeding events and 21.5% non-major bleeding events. Female gender, high-bleeding-risk surgical procedure, low-bleeding-risk surgical procedure and non-surgical interventions were associated with bleeding in hospitalized patients treated with anticoagulants.

The prevalence of bleeding observed in our inpatient population is higher than reported in a previous study in outpatients [26]. Linkins et al. evaluated VKA-related bleeding complications in patients who received oral anticoagulant therapy for at least 3 months. The authors analyzed thirty-three studies in this meta-analysis and included 10.757 patients who received anticoagulant therapy. The prevalence of major bleeding events was 2.6% (276 out of 10.757 patients). An explanation for the larger number of bleeding events in our population is that hospitalized patients are more vulnerable compared to outpatients due to start of additional medication influencing the metabolism of anticoagulants and because of (surgical) interventions. This is confirmed by the finding that the majority of bleeding events in our study occurred in surgical patients (16.1%), in comparison with non-surgical patients (2.2%).

Female gender was associated with bleeding in hospitalized patients treated with anticoagulants and is recognized before as risk factor of bleeding [27,28]. Cosma Rochat et al. found that after adjustment for patient characteristics (e.g. age), hospitalized women receiving oral anticoagulant therapy experienced a 4-fold increased risk of bleeding compared with men [27]. Patients who underwent a surgical procedure (high or low-bleeding-risk procedures) were more at risk of having a bleeding compared to patients who had no surgery. The management of bridging anticoagulation therapy in patients undergoing high and low-bleeding-risk surgical procedures is a complex process which could be an explanation of the increased risk of bleeding in surgical patients [14]. We found no increased risk of bleeding in patients who underwent a clinically non-relevant bleeding risk surgical procedure. Contrary to high and low-bleeding-risk surgical procedures, anticoagulant therapy can be continued in the perioperative period during clinically non-relevant bleeding risk procedures [14].

Non-surgical interventions were also associated with an increased risk of bleeding. A potential explanation for this increased risk of bleeding is confounding. An endoscopic intervention for example is important for the diagnosis and primary treatment of bleeding and is therefore used because of a bleeding event. This was confirmed by our results, because only one bleeding event occurred as a result of an endoscopic intervention.

The present study showed no association of combined VKA and LMWH treatment and the risk of bleeding. Because combined treatment is often used for a short period (e.g. postoperative), it is relatively safe for these patients [29].

Combination of single antiplatelet therapy (SAPT) with a VKA or DOAC or LMWH and combination of dual antiplatelet therapy (DAPT) with a VKA or DOAC or LMWH showed no increase of bleeding risk compared to patients using VKA monotherapy. This can be explained by the fact that antiplatelet therapy co-administered with anticoagulants most likely were prescribed to patients considered at decreased risk of

bleeding.

Furthermore, we found no significant difference in bleeding between patients using DOAC monotherapy and patients using VKA monotherapy. The use of DOACs was substantially less than VKAs in the Netherlands at the time of our study [30], which could be a possible reason for not finding a significant difference between DOAC and VKA users.

Several commonly cited risk factors of bleeding, such as advanced age [7,9,31,32] and prior bleeding [7,9,10] showed no association with an increased risk of bleeding in our study. These findings are consistent with Rochat et al., who attribute this to the uncertainty of their effect on the short-term risk of bleeding. The mean follow-up duration of eight days in our study confirmed that factors, such as advanced age and prior bleeding may not have a major impact on short-term bleeding risk [27].

We found no increased risk of bleeding in patients using concomitant interacting drugs with VKAs. These drugs inhibit the metabolism of VKAs by inhibiting the liver enzyme CYP2C9 and therefore an increased risk of bleeding was expected [33,34].

Furthermore, we expected to find more bleeding events in patients admitted to a University Medical Center compared to a general teaching hospital since patients may be transferred to a University Medical Center because of a high medical complexity, which may be accompanied by a high risk of bleeding. However, we found no difference in the prevalence of bleeding events between the two types of hospitals.

Stratified analysis for major bleeding events showed the same potential risk factors compared to the risk factors for any bleeding. This confirms the association with the identified risk factors.

4.1. Strengths and limitations

This study is the first study on the prevalence and potential risk factors of bleeding in hospitalized patients treated with anticoagulant therapy. Furthermore, the study was performed in two different types of hospitals, a University Medical Center and a general teaching hospital, which increases the generalizability of our findings. Another strength is the prospective design of the study. Finally, all bleeding events were evaluated and classified by two independent expert physicians in the field using internationally accepted ISTH criteria.

A few limitations of our study should be mentioned. First, data on bleeding were derived from reports of the responsible physicians noted in the electronic medical records (EMRs). This makes the study dependent on the information recorded by the responsible physician, which may lead to underreporting of the number of bleeding events. Second, the number of patients using concomitant interacting drugs was relatively low, decreasing the power to find significant associations between the use of concomitant interacting drugs and the risk of bleeding. Third, commonly used risk scores for bleeding such as the HAS-BLED score could not be used, as our patients are dissimilar to the study population this score was based on. Finally, this study was performed in patients using anticoagulants, without using a control group of patients who had a bleeding during hospitalization and did not use this type of drugs.

In conclusion, the prevalence of bleeding in anticoagulant users during hospitalization was 65 out of 906 patients (7.2%). This study detected potential risk factors that could help to identify patients on anticoagulants who have an increased risk of bleeding during hospitalization. These findings can be used to identify patients at the highest risk of bleeding. Doing so allows for targeted interventions for the multidisciplinary antithrombotic team to reduce bleeding risk during hospitalization.

Authors' contributions

ARD wrote the manuscript; all other co-authors commented on previous versions of the manuscript and agreed with the final content. ARD coordinated the study start-up and data collection. PMLAvdB designed the study. MJHAK, JD, RB and FWGL participated in the study design. FNC and EK assessed the bleeding events. All authors read and approved the final manuscript.

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Competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejim.2019.01.008.

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