Clinically relevant non-major bleeding with oral anticoagulants: non-major may not be trivial

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Introduction

The clinical benefit of anticoagulant treatment for various indications is offset by the risk of bleeding. The impact of bleeding related to vitamin K antagonist (VKA) use, in terms of patients' discomfort or temporary disability and in terms of both medical and socio-economic resources is not negligible[1-4]. However, the majority of studies have focused on major bleeding, used obsolete definitions of bleeding and have not distinguished between clinically relevant non-major bleeding (CRNMB) and minor events[2,3]. The International Society on Thrombosis and Haemostasis provided a standard definition of CRNMB in 2015 as those events that are not major but require any kind of medical intervention[5].

Over the last decade, many randomised phase III studies on direct oral anticoagulants (DOAC) have reported incidences of CRNMB in patients treated for atrial fibrillation or venous thromboembolism[6-14]. The rates of CRNMB in these studies have varied between 4 and 12%[15-17]. In the observational studies, the rates of major bleeding were about 5% and those of CRNMB varied between 10 and 20%[18-20]. Overall, compared with major bleeds, CRNMB tend to occur more frequently and are associated with a lower mortality[6-14,19]. However, the burden of care arising from CRNMB, for both the patient and the health system, is difficult to estimate in clinical practice.

We carried out a prospective, observational, multicentre, cohort study to assess the clinical characteristics, management and outcomes of CRNMB occurring in patients while on oral anticoagulants.

Materials and methods

Consecutive patients hospitalised for CRNMB occurring during treatment with either a DOAC or VKA were included in this study. CRNMB was defined according to the criteria set out by the International Society on Thrombosis and Haemostasis[5].

The following data were collected: each patient's features and comorbidities, indication for anticoagulant therapy, site of bleeding, symptoms on admission, haemodynamic parameters, relevant laboratory results (International Normalised Ratio [INR], haemoglobin count, renal function, etc.), medical treatment (red blood cells, plasma, haemostatic agents), interventions (surgery, endoscopy, endovascular treatment), duration of hospital stay and clinical status at discharge. The management of DOAC- and VKA-related CRNMB was at the discretion of the attending physicians.

The study protocol was approved by local Ethical Committees.

Frequency data are presented as proportions with 95% confidence intervals (95% CI). Continuous data are shown as means ± standard deviations (SD). Student`s *t*-test test and the χ^2 test were used for comparisons of continuous and categorical variables, respectively. Statistical analyses were performed using SPSS 21.0 (IBM Corporation, Armonk, NY, USA).

Results

Between September 2013 and August 2016, 205 patients were included in the study (50 taking a DOAC and 155 taking a VKA). The main indication for anticoagulant treatment was atrial fibrillation (81% of all patients) and the mean age of the patients was 78±11 years. The most prevalent comorbidities were hypertension, vascular disease, a history of bleeding, renal failure and heart failure. DOAC and VKA patients differed only by their prevalences of renal failure (12% *vs* 32%, respectively; p=0.006) (Table I).

The most commonly reported types of bleeding were macroscopic haematuria, skin or subcutaneous haematomas, epistaxis, rectal blood loss and muscle haematomas (Table II). The majority of bleeds occurred spontaneously, while 24% occurred after trauma or invasive medical procedures (Table I).

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Table I - Patients' features and bleeding sites.

	Overall N=205, n (%)	DOAC N=50, n (%)	VKA N=155, n (%)
Age, mean±SD	78±11	78±10	78±11
range	29-96	40-96	29-93
Male gender	112 (55)	33 (66)	79 (51)
Indication for anticoagulation			
Atrial fibrillation	166 (81)	47 (94)	119 (77)
Venous thromboembolism	11 (6)	3 (6)	10 (6)
Hypertension	144 (70)	32 (64)	112 (72)
Renal failure	55 (27)	6 (12)	49 (32)
Diabetes	40 (19)	11 (22)	29 (19)
Previous bleeding	62 (30)	15 (30)	47 (30)
Previous stroke	33 (16)	10 (20)	23 (15)
Heart failure	48 (23)	15 (30)	33 (21)
Vascular disease	69 (34)	13 (26)	56 (36)
Malignancy	32 (16)	9 (18)	23 (15)
NSAID/antiplatelet use	17 (9)	6 (12)	13 (8)
Site			
Gastrointestinal	49 (24)	20 (40)	29 (19)
Genitourinary	38 (18)	17 (34)	21 (13)
Respiratory tract	50 (24)	6 (12)	44 (28)
Intramuscular	23 (11)	1 (2)	22 (14)
Skin/subcutaneous	36 (18)	5 (10)	31 (20)
Other	9 (4)	1 (2)	8 (5)
Trauma	50 (24)	10 (20)	40 (26)

DOAC: direct oral anticoagulants; VKA: vitamin K antagonists; SD: standard deviation; NSAID: non-steroidal anti inflammatory drugs.

Table II - Management strategies and outcomes according to bleeding site.

Bleeding site	N	Type of bleeding	N	Clinical managment					Death N (%)
				Interruption of the drug N (%)	*Endoscopy N (%)*	*Procedures or surgery* N (%)*	*RBC N (%)*	*FFP/PCC*	
Gastrointestinal	49	Haematemesis	6	40 (82)	29 (59)	3 (6)	4 (8)	0/2	4 (8)
		Melaena	8						
		Rectal	29						
		Anaemia	6						
Respiratory tract	50	Haemoptysis	10	21 (42)	6 (12)	33 (66)	1 (2)	1/3	2 (4)
		Epistaxis	32						
		Gingival	2						
		Pleural	6						
Genitourinary	38	Macroscopic haematuria	36	32 (84)	10 (26)	5 (13)	1 (3)	1/1	1 (3)
		Genital	2						
Skin/subcutaneous	36		36	27 (75)	-	3 (8)	-	1/3	3 (8)
Intramuscular	23		23	19 (83)	-	11 (48)	-	0/3	-
Peritoneal/pelvic	8		8	8	1	3	-	0/4	
Parotid gland	1		1	1	-	-	-	-	

RBC: red blood cells; FFP: fresh-frozen plasma; PCC: prothrombin complex concentrates; *minor surgery or surgery for cancer.

On admission, anticoagulant therapy was interrupted in 148 patients (72% of all patients; 76 and 71% of DOAC and VKA patients, respectively). About 3% of patients were given one unit of red blood cells. Overall 19 patients, all taking VKA, received fresh-frozen plasma (3 patients) or prothrombin complex concentrates. Tranexamic acid was administered to five patients (3 DOAC patients).

Bleeding required minor surgery or interventional procedures in 92 cases (45%; 46 and 44% of DOAC and VKA patients, respectively): cauterisation or packing for nasal bleeding in 28 patients and endoscopy for gastrointestinal or genitourinary bleeding in 39 patients. The management and outcome of bleeding events are reported in Table II, divided according to site of bleeding. DOAC patients more frequently required endoscopy for the management of CRNMB, while VKA patients more frequently required angiography or other procedures (pleural drainage, nasal packing, and other).

Seven patients (4%) experienced a major cardiovascular event during their stay in hospital, most after gastrointestinal bleeding (Table III). These events were acute coronary syndrome (n=5), systemic embolism (n=1) and ischaemic stroke (n=1). None of these seven patients had been treated with prothrombin complex concentrates to manage their acute bleeding.

Ten patients died in hospital (5%; 6% of DOAC patients and 4% of VKA patients). The mean time to death was 7 days. Two patients died of heart failure (1 DOAC patient), two of acute coronary syndrome (1 DOAC patient), three of infections, two of respiratory failure and one of cancer.

The mean time spent in hospital was 8 days and was similar in DOAC and VKA patients (9 and 7 days, respectively).

Discussion

Our study results indicated that CRNMB occurring while on oral anticoagulant therapy and requiring hospitalisation are not trivial for either patients or health care systems. Specifically, these events frequently require interventions or pharmacological management, may necessitate blood transfusions and, most importantly, are associated with a far from negligible risk of death and/or major cardiovascular complications. In fact, in our study, 45% of patients with CRNMB required minor surgery or interventional procedures (46% of DOAC patients) and 4% of patients had a major cardiovascular complication (1 DOAC patient) during their stay in hospital. Data from the Dresden NOAC registry pertaining to 379 CRNMB showed that the majority of the bleeds could be managed conservatively and surgical or interventional treatment was required in only 51 cases (13.5%). Procedures in that study mainly consisted of sutures after traumatic skin lesions, cauterisation of mucosal bleeding, and endoscopic treatment of gastrointestinal bleeding[5]. Only one patient experienced a major cardiovascular event[5]. The differences between our results and those from the Dresden NOAC registry may be partially accounted for by the different designs of the two studies: our study was based on patients with CRNMB admitted to hospital while the Dresden registry also included outpatients.

Table III - Major cardiovascular events during hospitalisation after anticoagulant-associated clinically relevant, non-major bleeding.

Type of CV event	Gender/ age (years)	Indication for anticoagulants	Type of drug	Site of bleeding	Procoagulants/ transfusions	Interruption of the drug	Time from bleeding (days)	Death
Acute coronary syndrome	M 70	Non-valvular AF	VKA	Lower gastrointestinal (rectal)	None/none	Yes	1	No
	F 87	Non-valvular AF	VKA	Upper gastrointestinal (haematemesis)	None/none	Yes	1	No
	F 90	Non-valvular AF	DOAC	Lower gastrointestinal (rectal)	None/none	Yes	1	Yes
	F 83	VTE	VKA	Muscle haematoma	Vit K/none	Yes	2	No
	M 77	Non-valvular AF	VKA	Haemoptysis	Vit K/none	Yes	1	Yes
Ischaemic stroke	M 82	Other	VKA	Epistaxis	None/none	Yes	NA	No
Systemic embolism	M 82	Non-valvular AF	VKA	Upper gastrointestinal (haematemesis)	Vit K/none	Yes	2	No

CV: cardiovascular; AF: atrial fibrillation; VTE: venous thromboembolism; VKA: vitamin K antagonist; DOAC: direct oral anticoagulant; Vit K: vitamin K; NA: not available.

However, CRNMB not requiring surgery or interventional procedures can be considered clinically relevant because it causes distress to the patient and can lead to temporary interruption of anticoagulant therapy; such an interruption can contribute to the risk of arterial or venous embolic complications, as observed in our study.

Our study results support previous findings on differences between DOAC and VKA in terms of organ-specific bleeding patterns. In fact, gastrointestinal and genitourinary CRNMB were more common among patients taking DOAC than among those taking VKA, whereas upper airway bleeding and intramuscular haematomas were more common in VKA patients than in DOAC patients. As a consequence, strategies for management of bleeding events differed between DOAC and VKA patients.

This study had some limitations. First of all, only patients hospitalised for CRNMB were studied. This selection of events with a more severe clinical presentation and course, and probably greater utilisation of healthcare resources, may have led to a bias. A significant proportion of patients experiencing CRNMB are managed as outpatients in real-life[19]. Moreover, this was an observational study and results from comparisons between DOAC and VKA patients should be interpreted with caution, as the number of DOAC-related events was limited and all therapeutic decisions were left to the discretion of the attending physicians.

Conclusions

In terms of management, duration of hospitalisation and in-hospital mortality, the burden arising from CRNMB occurring in clinical practice in patients taking DOAC or VKA was not trivial. Our study confirms the value of the recent definition of CRNMB by the International Society on Thrombosis and Haemostasis.

Authorship contributions

LF contributed to the interpretation of data, drafting and critical revision of the manuscript as well as supervision of all statistical analyses and is the guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article; CB contributed to the conception and design of the study, to the interpretation of data, and to the drafting and critical revision of the manuscript; SV, RS, CN, GM, LM, FP, SC, RC, RR and GA contributed to the interpretation of data, and to the drafting and critical revision of the manuscript.

Keywords: anticoagulants, bleeding, clinically relevant non-major bleeding, direct oral anticoagulants (DOACs), vitamin K antagonists (VKAs).

Disclosure of conflicts of interest

LF, SV, RS, CN, GM, LM, FP, SC, RC and RR have nothing to disclose. CB reports lectures fees from Boehringer Ingelheim and Bayer HealthCare, outside the submitted work. GA reports lectures fees from Boehringer Ingelheim, Sanofi, Bayer HealthCare, and Daiichi-Sankyo, outside the submitted work.

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