

Do women with venous thromboembolism bleed more than men during anticoagulation? Data from the real-life, prospective START-Register

Gualtiero Palareti¹ , Cristina Legnani, Emilia Antonucci, Benilde Cosmi, Anna Falanga, Daniela Poli, Daniela Mastroiacovo, Vittorio Pengo, Walter Ageno and Sophie Testa

Abstract

Background: Venous thromboembolism (VTE) is a frequent and serious disease that requires immediate and long-term anticoagulant treatment, which is inevitably associated with a risk of bleeding complications. Some studies, though not all, reported a higher risk of bleeding in female patients treated with either old anticoagulants [vitamin k antagonists (VKAs)] or recent anticoagulants [direct oral anticoagulants (DOACs)]. Furthermore, analyses of clinical trials reported an abnormal vaginal bleeding in women of reproductive age treated with DOACs. This study aimed at comparing the risk of bleeding in an inception cohort of VTE women and men included in a prospective observational registry.

Methods: Baseline characteristics and bleeding events occurring during anticoagulation in patients of both sexes, included in the START-Register after a first VTE, were analyzed.

Results: In all, 1298 women were compared with 1290 men. Women were older and more often had renal diseases; their index events were often provoked (often by hormonal contraception and pregnancy), and more frequently presented as isolated pulmonary embolism (PE). The rate of bleeding was similar in women (2.9% patient-years) and men (2.1% patient-years), though it was higher when uterine bleeds were included (3.5% patient-years, $p=0.0141$). More bleeds occurred in VKA- than DOAC-treated patients (6.4% versus 2.6%, respectively; $p=0.0013$). At multivariate analysis, age ≥ 75 years was associated with higher prevalence of bleeds.

Conclusion: The occurrence of bleeding was not different between women and men during anticoagulation after VTE. Only after inclusion of vaginal/uterine bleeds, the rate of bleeding was higher in women. The incidence of bleeding was higher in women treated with VKAs.

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Correspondence to:

Gualtiero Palareti
‘Arianna Anticoagulazione’
Foundation, Via Paolo
Fabbri, 1/3, 40138
Bologna, Italy.
Gualtiero.palareti@unibo.it
unibo.it

Cristina Legnani
Emilia Antonucci
‘Arianna Anticoagulazione’
Foundation, Bologna, Italy

Benilde Cosmi
Unit of Angiology & Blood
Coagulation, Department
of Specialty, Diagnostics
& Experimental Medicine,
University Hospital, IRCCS,
Bologna, Italy

Anna Falanga
Dipartimento di
Medicina e Chirurgia,
Università Milano
Bicocca, Milan, Italy; UOC
Immunematologia e
Medicina Trasfusionale
ASST, Bergamo, Italy

Daniela Poli
SOD Malattie
Aterotrombotiche, Azienda
Ospedaliero Universitaria-
Careggi, Firenze, Italy

Daniela Mastroiacovo
Dipartimento di Angiologia,
Ospedale SS. Filippo e
Nicola, Avezzano, Italy

Vittorio Pengo
Thrombosis Research
Laboratory, University of
Padua, Padua, Italy

Walter Ageno
Dipartimento di
Emergenza e Accettazione,
Centro Trombosi ed
Emostasi, Ospedale
di Circolo, Università
dell’Insubria, Varese, Italy

Sophie Testa
Centro Emostasi e
Trombosi A O Istituti
Ospitalieri di Cremona,
Cremona, Italy

Plain Language Summary

The risk of bleeding in women anticoagulated for deep vein thrombosis or pulmonary embolism is not higher than that in men, except for vaginal bleeding

Background: The occurrence of a venous thromboembolic event (VTE, including deep vein thrombosis and pulmonary embolism) necessarily requires a period of at least 3–6 months of treatment with anticoagulant drugs [either vitamin k antagonists (VKA) or, more recently, direct oral anticoagulants (DOACs)]. Anticoagulation therapy, however, is associated with a risk of bleeding that is influenced by several factors. Sex is one of these factors as some authors have hypothesized that women are at higher risk than men. Furthermore, some studies have recently found more vaginal bleeding in VTE women treated with a DOAC compared with those who received VKAs.

Methods: The present study aimed to compare the frequency of bleeds occurring in women and in men who were treated with DOACs or VKAs for a first VTE event and followed in real-life conditions. Since the beginning of their anticoagulant treatment, the patients were included in a prospective, multicenter, observational registry (the START-Register), and bleeding events were recorded.

Results: A total of 1298 women were compared with 1290 men. Women were older and more often were affected by renal diseases; their VTE events were often associated with risk factors (especially hormonal contraception and pregnancy) and presented as isolated pulmonary embolism. The rate of all bleeding events (including major, non-major but clinically relevant, and minor bleeds) was higher in women (3.5% patient-years) than in men (2.1% patient-years, $p=0.0141$); however, the difference was no longer statistically significant after exclusion of uterine bleeds (2.9% patient years). More bleeding occurred in women receiving VKA as anticoagulant drug compared with those treated with a DOAC (6.4% versus 2.6%, respectively; $p=0.0013$). At multivariate analysis, age ≥ 75 years was associated with higher prevalence of bleeds.

Conclusion: In conclusion, we found that in real-life conditions, the rate of bleeding events occurring during anticoagulation after a VTE episode is not higher in women than in men. Only after inclusion of vaginal bleeds, the rate of bleeding was higher in women. More bleeds (including vaginal bleeding) occurred in women treated with VKA than DOACs.

Keywords: women, bleeding, anticoagulation, venous thromboembolism

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Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE) is a frequent and serious disease, potentially life-threatening in the acute phase, with long-lasting sequelae and a permanent risk of recurrent events which, in turn, lead to all the above complications. All patients with a first VTE event need an immediate anticoagulant treatment that should last 3–6 months (initial and maintenance period) to adequately treat the event; whereas only some of them, with high risk of recurrences and non-high risk of bleeding, deserve an extension of anticoagulant treatment finalized to lower the risk of recurrences. Although, with differences depending on the drugs and their dosage used, all anticoagulant treatments are associated with a risk of bleeding. Sex is one of the several factors which potentially may be involved in determining the risk of bleeding during anticoagulant treatments. Female sex was found to be significantly associated with bleeding events in hospitalized patients treated with different types of anticoagulants.¹ Conversely, female sex was not a significant factor for bleeding in outpatients treated with VKAs (vitamin k antagonists) in the historical ISCOAT cohort,² as well as in a more recent cohort³ and other studies.⁴ Furthermore,

female sex was not included among the risk factors (RFs) for bleeding in international guidelines regarding VKA use.⁵ Little information is available about sex-related differences in the safety of direct oral anticoagulant (DOAC) use in VTE patients. The results of meta-analyses of the available studies, mainly interventional trials, were inconsistent for this point.^{6–8} Recent results of analysis of interventional studies,^{9,10} though not all,¹¹ reported an abnormal vaginal bleeding in women of reproductive age treated with a DOAC. Unfortunately, data from observational studies specifically dedicated to these issues are scanty. Only recently, an observational study has been published reporting data on uterine bleeding after exposure to DOACs in women included in four databases in the United States. The study reported an increased risk of uterine bleeding in women treated with rivaroxaban or apixaban.¹²

The present study aimed at analyzing the risk of bleeding complications occurring in female or male patients affected by a VTE episode, who were included in the prospective, observational, multicenter START-Register and followed during oral anticoagulant treatments. The baseline characteristics of women, type of management, and clinical results were

analyzed and compared with those recorded in men; furthermore, the results recorded in women treated with DOACs were compared with those treated with VKAs.

Materials and methods

The START-Register

The present article reports on patients included in the START-Register for a first VTE event. The START-Register (ClinicalTrials.gov identifier: NCT02219984) is an observational, prospective, multicenter, dynamic cohort study of adults (≥ 18 years) starting anticoagulation therapy, whatever the indication for treatment and drug/dosage used.¹³ The START-Register was authorized by the Ethical Committee of the University Hospital 'S. Orsola-Malpighi', Bologna, Italy, on October 2011 (N=142/2010/0/Oss"). The registry, one of the activities of the 'Arianna Anticoagulazione' Foundation (Bologna, Italy), is open to all physicians prescribing anticoagulant or antithrombotic therapy who agree to the registry protocol. Participants should obtain approval from their local Institution Review Board and are required to enroll their patients, after receiving their informed consent, consecutively or randomly, with no exclusion criteria other than obstacles for follow-up (short life-expectancy or geographical inaccessibility). The accuracy and completeness of the data collected anonymously in the central electronic database are checked by a trained and dedicated monitor figure who also solicits participating centers to contact, for the purpose of this study, patients lost to follow-up either by a telephone call or through their General Practitioner. The study was carried out and is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies.¹⁴

Study population

The present study examined patients with a first episode of DVT of a lower limb or PE, who were included in the START-Register from January 2011 to September 2020. The types of treatment and the events occurring during follow-up were then analyzed in female and male patients. Low molecular weight heparins (LMWHs), fondaparinux, and VKAs (warfarin was used in about 99% of patients) were always available as anticoagulant drugs for therapy during the observation

period, whereas DOACs have only been allowed and reimbursed by the National and Regional Health Systems for initial, long-term, and extended anticoagulant treatment for patients with VTE since January 2014.

Data collection

Participants in the START-Register connect to the central electronic database *via* web using individual passwords. Information is recorded in structured case report form (CRF) and involves baseline characteristics of included patients and their follow-up. Baseline characteristics of patients included in the study were (a) demographic, body weight, routine laboratory data, past medical history; (b) characteristics of index VTE event and presence of RFs; (c) anticoagulant agents used, dosages, or the intended therapeutic range [2.0–3.0 INR (International Normalized Ratio) in all cases receiving VKAs], concomitant medications (especially antiplatelet drugs). Patients were considered 'fragile' when their age was > 75 years or body weight ≤ 50 kg or creatinine clearance < 50 ml/min¹⁵). Serum creatinine levels were measured by local hospital laboratories, and creatinine clearance (CrCl) calculated by the Cockcroft–Gault formula.¹⁶ Renal failure (CrCl < 60 ml/min) was defined according to National Kidney Foundation stratification.¹⁷

Information on index events

Information was collected about the nature and site of index VTE events, that were classified as (a) unprovoked, when not temporally associated with any potential triggering conditions or RFs; (b) associated with weak RF, such as minor, arthroscopic or laparoscopic general surgery, pregnancy or puerperium, contraceptive or replacement hormonal therapy, long trip, minor trauma, stay in hospital, reduced mobility (not complete immobilization); (c) provoked by transient major RF, when in association with one of the following conditions occurring within 3 months of VTE diagnosis: major surgery with general or spinal anesthesia, lower limb fracture, casting or no weight bearing for ≥ 3 days, bed-bound for > 3 days due to acute illness, and so on; (d) provoked by permanent major RF, when associated with active cancer, paraplegia, chronic active inflammatory disease (e.g. intestinal inflammatory disease) or other chronic serious diseases, serious inherited thrombophilic

alterations, antiphospholipid syndrome, severe post-thrombotic syndrome, presence of cava filter. The site of events was classified as (a) cases with DVT [either proximal or isolated distal (IDDVT)], when thrombosis of deep veins was not associated with diagnosis of PE; or (b) cases with PE, when a PE event was associated with DVT, or was isolated.

Follow-up data

Follow-up was considered from inclusion of patients until December 2020, or until a permanent cessation of anticoagulant treatment, the last follow-up available in patients who subsequently were lost to follow-up or declined to further participate in the START-Register, or occurrence of major bleeding (MB), thrombotic complications, death, whichever came first. During follow-up, detailed clinical reports of any relevant clinical outcome occurring in enrolled patients were collected. MB was defined according to International Society on Thrombosis and Haemostasis criteria.¹⁸ Clinically relevant non-major bleeding (CRNMB) events were defined as any overt bleeding requiring a medical intervention or treatment discontinuation, not meeting any of the criteria for MB.¹⁹ Minor bleeds were defined as the bleeding events reported by the patients who did not have the characteristics of MB or CRNMB. To evaluate the intensity of menstrual bleeding, we invited the START-Register participants to ask women about duration and intensity of menstruations during anticoagulation compared with the last menstruation before anticoagulation was started.²⁰

Statistical analysis

Continuous variables are expressed as median with interquartile range (IQR). Categorical variables are expressed as frequencies and percentages. The number of bleeding events was expressed as percentage and incidence rate, calculated as the number of events per 100 patient-years of observation. Differences between groups were assessed using the χ^2 test with Yates' correction for categorical variables and the Mann-Whitney *U* test for continuous variables. The data were analyzed with the use of Prism software (Version 8.4.0, GraphPad Software Incorporated, San Diego, CA, USA), and Stata, version 14 statistical software package (Stata Corp., College Station, TX, USA) was used for

data processing. Cox regression analysis was performed by entering individual variables considered as RF for bleeding events: female sex, age (≥ 75 versus < 75 years), renal failure (< 60 versus ≥ 60 ml/min), active cancer, hypertension, previous bleeding events, alcohol consumption, anti-platelet drugs, hemoglobin level reduction (≤ 10 versus > 10 g/dl), platelet count reduction ($< 100 \times 10^3$ versus $\geq 100 \times 10^3 \mu\text{l}$). The SPSS software for Windows, version 22 (SPSS Inc., College Station, TX, USA) and Stata, version 14 statistical software package (Stata Corp.) were used for data processing.

Results

Baseline characteristics of patients and treatments

The present study analyzed 2588 patients (Figure 1), comprising 1298 women and 1290 men, who were enrolled in the START-Register by physicians active in 37 Italian clinical centers, when anticoagulation was started after a first VTE event. As shown in Table 1, women were significantly older than men ($p < 0.0001$), more women being ≥ 75 years old than men (43.0% versus 26.9%, respectively, $p < 0.0001$). The renal function, measured by the CrCl, was in general worse in females than men; significantly more women had CrCl levels < 30 ml/min ($p = 0.0002$) and $30\text{--}59$ ml/min (< 0.0001) than men. The type of index event was more commonly a proximal DVT in patients of both sexes; however, the occurrence of an isolated PE event was more frequent in women (26.5% versus 19.1%; $p < 0.0001$). Among women with isolated PE, 75 were aged ≤ 50 years and the index event in half of them ($n = 38$) occurred in association with hormonal contraception (HC). The index event was unprovoked more frequently in men (73.5% versus 60.7%; $p < 0.0001$). Among patients with provoked events, the association with weak RFs (mainly HC and pregnancy) was significantly more prevalent among women ($p < 0.0001$), who also presented some cases with concurrence of different factors (HC or pregnancy with other weak and transient factors). Hypertension was more frequent in women than in men (49.3% versus 44.0%; $p = 0.0069$). The proportion of fragile patients was significantly higher among women than men (27.9% versus 11.5%; $p < 0.0001$). No significant differences were

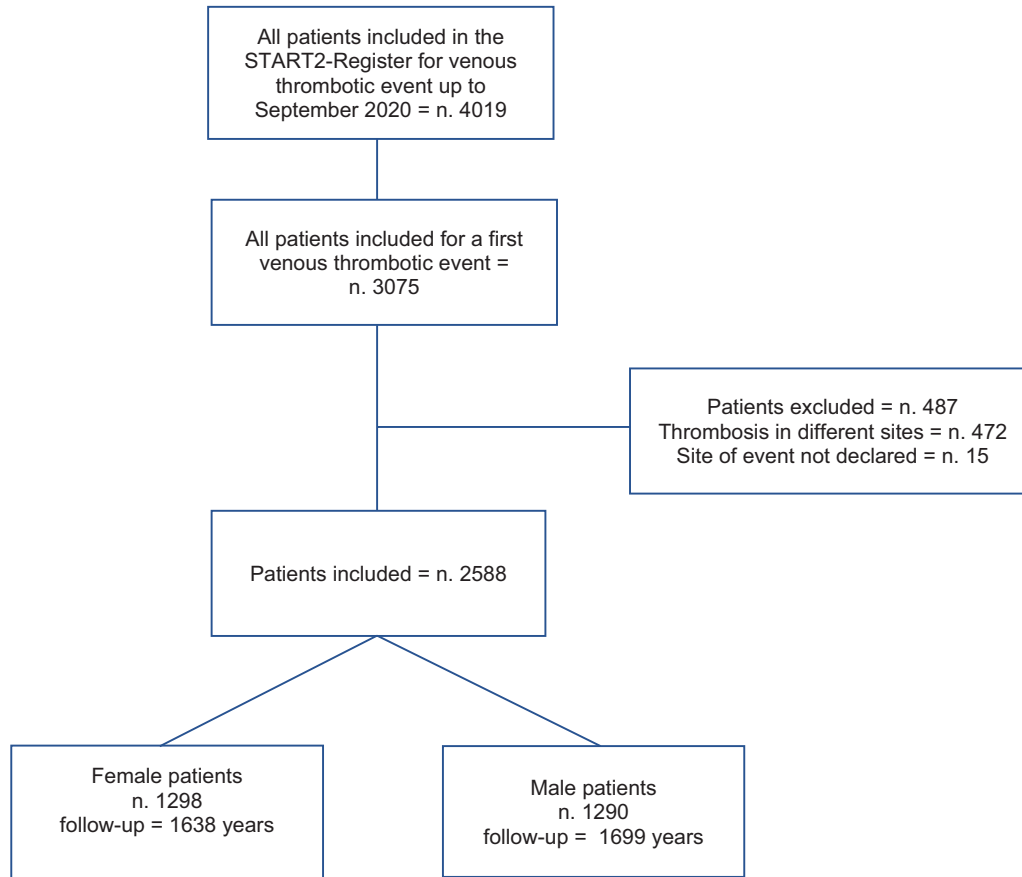


Figure 1. Patient flowchart.

detected as regards others associated clinical characteristics.

In general, the anticoagulant drugs used were not different between sexes (Table 2). Among the DOACs, rivaroxaban was the more largely used because it was the first one allowed and reimbursed by the National and Regional Health Systems for VTE treatment. The low-dose DOACs were prescribed more frequently in women than in men (20.0% *versus* 9.1%; $p < 0.0001$). No differences were found regarding other associated treatments except for a more frequent use of antiarrhythmic drugs in women ($p = 0.0019$).

Bleeding events during anticoagulant therapy

The occurrence of bleeding complications during treatment in women and men is shown in detail in Table 3. The incidence of all bleeds (major, CRNMB, and minor) was significantly higher in female patients (3.5% *versus* 2.1% patient-years,

respectively; $p = 0.0141$); relative risk of women *versus* men = 1.7, confidence interval (CI), 1.1–2.7; $p = 0.01$; however, the difference was no longer statistically significant after exclusion of the vaginal bleeds (2.9% patient-years). Three bleeding events were fatal in women and two in men (four for intracranial hemorrhage). More bleeding events (of all types) occurred in women treated with warfarin than with DOACs (6.4% *versus* 2.6%, respectively; $p = 0.0013$); relative risk: 2.44 (95% CI, 1.38–4.32; $p = 0.0022$). The bleeds were significantly more frequent in women of young (≤ 50 years) and middle age (51–74 years) classes than in men of the same age classes and occurred especially during the first 3 months of treatment in both sexes. Eleven abnormal vaginal bleeds were reported during follow-up, 8 of whom in women treated with VKAs. With the exception of one, all vaginal bleeding occurred in women aged ≤ 50 years: seven cases in women treated with warfarin (4.4% patient-years) (two of them classified as CRNMB) and three (2.4% patient-years,

Table 1. Baseline characteristics of examined patients.

All patients	Females <i>n</i> = 1298	Males <i>n</i> = 1290	<i>p</i>
Age, median (IQR), years	72 (53–81)	65 (52–75)	<0.0001
Age classes, <i>n</i> (%)			
≤50 years	308 (23.7)	293 (22.7)	0.5469
51–74 years	459 (33.3)	688 (50.4)	<0.0001
≥75 years	531 (43.0)	309 (26.9)	<0.0001
BMI, median (IQR)	26.0 (22.9–29.0)	26.5 (24.2–29.3)	<0.0001
Missing	10	4	
Creatinine clearance, <i>n</i> (%)			
<30 ml/min	48 (3.7)	18 (1.4)	0.0002
30–59 ml/min	438 (33.8)	231 (17.9)	<0.0001
≥60 ml/min	809 (62.5)	1039 (80.7)	<0.0001
Missing	3	2	
Type of VTE event, <i>n</i> (%)			
DVT			
Proximal	455 (35.1)	544 (42.2)	0.0002
Isolated distal	208 (16.0)	212 (16.4)	0.7825
PE (± DVT)			
PE + DVT	291 (22.4)	288 (22.3)	0.9513
Isolated PE	344 (26.5)	246 (19.1)	<0.0001
Nature of VTE events, <i>n</i> (%)			
Unprovoked	780 (60.7)	947 (73.5)	<0.0001
Provoked by: <i>n</i> (%)	505 (39.3)	341 (26.5)	
• weak RFs (HC <i>n</i> = 126, pregnancy <i>n</i> = 21)	193 (15.0)	32 (2.5)	<0.0001
• transient major RFs	181 (14.1)	183 (14.2)	0.9420
• permanent major RFs	103 (8.0)	126 (9.8)	0.1090
• >factors (HC <i>n</i> = 20, pregnancy <i>n</i> = 8)	28 (2.2)	0	<0.0001
Missing	13	2	
Diabetes, <i>n</i> (%)	128 (9.9)	126 (9.8)	0.9320
Hypertension, <i>n</i> (%)	640 (49.3)	568 (44.0)	0.0069

(Continued)

Table 1. (Continued)

All patients	Females n = 1298	Males n = 1290	p
IHD, CVD, PAD, n (%)	194 (14.9)	219 (17.0)	0.1446
Heart failure, n (%)	42 (3.2)	38 (2.9)	0.6573
Chronic inflammatory disease, n (%)	80 (6.2)	63 (4.9)	0.1488
Known thrombophilia, n (%)	96 (7.4)	109 (8.4)	0.3457
Hemoglobin level (≤10 g/dl)	84 (6.5)	22 (1.7)	<0.0001
Missing	9	12	
Fragile, n (%) ^a	362 (27.9)	148 (11.5)	<0.0001

BMI, body mass index; CVD, cerebrovascular disease; DVT, deep vein thrombosis; HC, hormonal contraception; IHD, ischemic heart disease; IQR, interquartile range; PAD, peripheral artery disease; PE, pulmonary embolism; RF, risk factors; VTE, venous thromboembolism.
 Statistically significant p values (< 0.05) are depicted in bold.
^aAge > 75 years or body weight ≤ 50 kg or creatinine clearance < 50 ml/min.

Table 2. Treatments of patients during follow-up.

All patients	Females n = 1298	Males n = 1290	p
Anticoagulation treatments			
• LMWHs, [or Fondaparinux], at therapeutic dosages, n (%)	71 (5.5)	68 (5.3)	0.8220
Duration, median (IQR), months	4.7 (2.4–14.2)	6.2 (2.7–13.4)	0.6298
• Warfarin, n (%)	613 (47.2)	563 (43.6)	0.0659
Duration, median (IQR), months	12.3 (5.9–27.1)	13.2 (6.5–27.6)	0.0989
• DOACs, n (%)	614 (47.3)	659 (51.1)	0.0532
Duration, median (IQR), months	8.8 (4.8–16.5)	9.8 (5.2–17.8)	0.2483
Apixaban, n (l.d.: 2.5 mg BID)	165 (61)	132 (33)	
Dabigatran, n (l.d.: 110 mg BID)	71 (17)	83 (7)	
Edoxaban, n (l.d.: 30 mg OID)	60 (20)	54 (9)	
Rivaroxaban, n (l.d.: 15 mg OID) ^a	309 (23)	384 (10)	
Patients treated with l.d. DOAC, n (%)	121 (20.0%)	59 (9.1%)	<0.0001
Missing	9	6	
Associated treatments, n (%)			
• Antiplatelet drugs	94 (7.3)	81 (6.3)	0.3125
• Antiarrhythmic drugs	53 (4.1)	26 (2.0)	0.0019
• Lipid lowering drugs	206 (15.9)	204 (15.8)	0.9445

BID, twice a day; DOAC, direct oral anticoagulant; IQR, interquartile range; l.d., low dose; LMWH, low molecular weight heparin and fondaparinux; OID, once a day.
 Statistically significant p values (< 0.05) are depicted in bold.
^aAll patients who were treated with low-dose rivaroxaban received one 15 mg tablet per day.

Table 3. Bleeding complications occurring during therapy.

	Females <i>n</i> = 1298	Males <i>n</i> = 1290	<i>p</i> ^a
Total follow-up, years	1638	1699	
Median FU (IQR), mo.	9.8 (5.1–20.4)	11.5 (5.7–21.8)	0.0710
All bleeds, <i>n</i> (%) [% pt-ys]	58 (4.5) [3.5]	35 (2.7) [2.1]	0.0141
All bleeds, vaginal excluded, <i>n</i> (%) [% pt-ys]	47 (3.6) [2.9]	35 (2.7) [2.1]	0.1384
Major and CRNMB, <i>n</i> (%) [% pt-ys]	24 (1.8) [1.5]	20 (1.5) [1.2]	0.4524
Minor bleeds, <i>n</i> (%) [% pt-ys]	23 (1.8) [1.4]	15 (1.2) [0.9]	0.1749
LMWH (F: ys. 62; M: ys. 58)	3 [4.8]	1 [1.7]	0.3443
Warfarin (F: ys. 928; M: ys. 917)	31 [3.3]	22 [2.4]	0.2457
DOACs (F: ys. 648; M: ys. 724)	13 [2.0]	12 [1.7]	0.6800
All vaginal bleeds, <i>n</i> (%) [% pt-ys]	11 (0.8) [0.7]		
Age ≤ 50years (<i>n</i> =308; ys. 293)	10 (3.2) [3.4]		
LMWH (<i>n</i> =14; ys. 6)	0		
Warfarin (<i>n</i> =147; ys. 160)	7 ^b (4.8) [4.4]		
DOACs (<i>n</i> =147; ys. 127)	3 (2.0) [2.4]		0.3617 ^c
All bleeds in women anticoagulated with warfarin versus DOAC (%)	6.4% versus 2.6%		0.0013^d
All bleeds in women treated with DOACs (%)			
With standard dose (<i>n</i> =493)	13 (2.6)		
With low dose (<i>n</i> =121) ^e	3 (2.5)		
Site of bleeds, <i>n</i> of M + CRNMB (minor)			
ICH	9 [2 deaths]	5 [2 deaths]	
GIH	6 [1 death] [4]	7 [3]	
Hb reduction > 2g/dL	5 (0)	3 (0)	
Hematuria	0 (4)	3 (4)	
Other	4 (15)	2 (8)	
Vaginal	2 (9)	–	
Distribution of all bleeds according to age, <i>n</i> (%)			
≤50years	13 (4.2)	3 (1.0)	0.0145
51–74years	20 (4.6)	14 (2.1)	0.0202
≥75years	25 (4.5)	18 (5.2)	0.6311

(Continued)

Table 3. (Continued)

	Females <i>n</i> = 1298	Males <i>n</i> = 1290	<i>p</i> ^a
Temporal distribution of all bleeds during AC, <i>n</i> (%)			
≤90 d.	17 (10.1)	11 (8.1)	0.5497
91–180 d.	10 (4.3)	4 (1.8)	0.1271
>180 d.	31 (3.4)	20 (2.1)	0.0878
Deaths during follow-up, <i>n</i> (%)			
Cancer, IHD, bleeding, other, <i>n</i>	25, 11, 3, 51	28, 11, 2, 41	
Lost to follow-up, <i>n</i> (%)			
	18 (1.4)	13 (1.0)	
<p>AC, anticoagulation; CRNMB, clinically relevant non-major bleeding; DOAC, direct oral anticoagulant; F, females; FU, follow-up; GIH, gastro-intestinal hemorrhage; ICH, intracranial hemorrhage; IHD, ischemic heart disease; IQR, interquartile range; LMWH, low molecular weight heparin and also includes fondaparinux; M, males; pt-ys, patient-years; ys, years.</p> <p>Statistically significant <i>p</i> values (< 0.05) are depicted in bold.</p> <p>^aCalculated on duration of FU if no differently declared.</p> <p>^bTwo vaginal bleeds were classified as CRNMB.</p> <p>^cComparison between vaginal bleeds occurring in warfarin- or DOAC-treated women.</p> <p>^dCalculated on the number of patients.</p> <p>^eNo vaginal bleeds.</p>			

Table 4. Risk factors for bleeding complications (with exclusion of vaginal bleeding): univariate and multivariate analysis.

Risk factors	Univariate		Multivariate	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Female sex	1.3 (0.8–2.1)	0.2	1.2 (0.7–7.9)	0.4
Age (≥75 versus <75 years)	1.9 (1.3–2.9)	0.001	1.5 (1.1–2.3)	0.04
Renal failure (<60 versus ≥60 ml/min)	2.0 (1.3–3.1)	0.001	1.1 (0.7–2.0)	0.6
Active cancer	1.9 (1.1–3.6)	0.04	1.7 (0.9–3.4)	0.08
Hypertension	2.1 (1.3–3.4)	0.001	1.5 (0.9–2.4)	0.1
Previous bleeding events	1.9 (0.7–5.4)	0.2	1.3 (0.4–3.8)	0.6
Alcohol consumption	1.7 (0.9–3.3)	0.1	1.9 (0.9–3.8)	0.07
Antiplatelet drugs	2.4 (1.3–4.6)	0.005	1.7 (0.9–3.3)	0.09
Hemoglobin level reduction (<10 versus ≥10 g/dl)	2.1 (1.0–4.9)	0.06	2.0 (0.9–4.6)	0.1
Platelet count reduction ^a (<100 × 10 ³ versus ≥100 × 10 ³ μl)	–	–	–	–
<p>CI, confidence interval; OR, odds ratio.</p> <p>Statistically significant <i>p</i> values (< 0.05) are depicted in bold.</p> <p>^aNo one patient had platelet count < 100 × 10³ μl.</p>				

difference, n.s.) in DOAC-treated women, all receiving standard dose rivaroxaban. At multivariate analysis (Table 4) only older age (≥ 75 versus < 75 years) resulted independently associated with bleeding complications ($p = 0.04$).

Discussion

The main purposes of the present study were to assess the risk of bleeding in women compared with men during treatment with oral anticoagulants for a VTE event in a setting of real-life conditions, and whether the risk of bleeding in women could be different depending on the type of anticoagulant drug used (VKAs or DOACs). The study analyzed the information collected in the prospective, observational, multicenter START-Register, in which all decisions about treatment of patients were left to the discretion of the treating physicians. Important results of the present study were (a) the incidence of all bleeding events (major, CRNMB, minor) was significantly higher in female than male patients but only if the vaginal bleeds were included in the evaluation; (b) the incidence of bleeding was significantly higher in females treated with VKAs than DOACs; (c) only 11 episodes (9 classified as minor bleeds) of vaginal bleeding were reported, 8 in warfarin (2 CRNMB) and 3 in DOAC-treated women (difference, n.s.); (d) finally, bleeds (of all types) were more frequent in young females than males and especially occurred during the first 3 months of treatment.

The study examined a relevant and similar number of both sex patients. Some differences, statistically and clinically significant, were detected between female and male patients. Women were older, more often had signs of renal impairment (about 37% of them had a CrCl < 60 ml/min, versus 19% in males), and more frequently were in a frailty condition. All the above characteristics may explain the physicians' preference for low-dose treatments in women receiving a DOAC (about 20% of them, more than double than in men).

The occurrence of bleeding complications during treatment was the major target of the study. Altogether, we found that the incidence of bleeding was in general low either in women or men (2.9% and 2.1% patient-years, respectively, n.s.); the incidence became significantly higher in women (3.5% patient-years, $p = 0.0141$) only

when the vaginal bleeds were included in the calculation. The incidence MB and CRNMB (two of the latter were abnormal vaginal bleeding) was rather low and similar between women and men (1.5% versus 1.2% patient-years, respectively, n.s.). After exclusion of uterine bleeding, only older age was found a significant RF for bleeding at multivariate analysis. Our findings are in contrast with the results of some meta-analytical studies which mainly investigated the interventional trials comparing use of DOACs or warfarin in VTE patients. In comparison with our results, these studies found substantially higher rates of MB + CRNMB in patients treated with warfarin or DOACs, and rates of bleeding significantly higher in females than in males. Alotaibi *et al.*,⁶ in their 'sex-based meta-analysis', found rates of MB + CRNMB significantly higher in women (11.1%) than in men (8.5%, $p = 0.0006$) treated with DOACs. Dentali *et al.*,⁸ in a meta-analysis of the interventional studies, found MB + CRNMB rates of 8.6% in women and 5.5% in men treated with DOACs ($p < 0.0001$). Very similar results were reported by Loffredo *et al.*⁷ We are not aware of other observational, real-life studies which reported data on this issue and therefore cannot make any comparison with our results. It is not easy to explain such differences in bleeding results between the interventional studies and the present observational study. Most clinical centers participating in the START-Register were anticoagulation clinics involved in the FCSA (the Italian Federation of Anticoagulation Clinics), particularly experienced in management of anticoagulated patients; they routinely follow the patients with periodical visits, give them the necessary education to the anticoagulant treatment and instruction to improve its outcomes. Another potential explanation is that a non-negligible portion of our patients (especially women) were receiving low-dose DOACs, expected to carry a lower risk of bleeding.

Uterine bleeding during anticoagulation for VTE is not uncommon. Recent results from the RIETE Registry reported a 0.1% of MB and 0.37% of CRNMB.²¹ Furthermore, studies deriving either from interventional trials or outpatient cohorts have pointed out an increased risk of abnormal vaginal bleeding in VTE women of reproductive age treated with DOACs, especially factor Xa inhibitors. An increased risk of vaginal bleeds was found in women treated with rivaroxaban,²²⁻²⁴ edoxaban,¹⁰ or apixaban.⁹

Conversely, a reduced risk of abnormal uterine bleeding was found in women receiving dabigatran (a factor IIa inhibitor) compared with warfarin.¹¹ A recent study,²⁰ which investigated the menstrual bleeding in women included in the EINSTEIN-CHOICE trial, did not find statistically significant differences between those treated with 20 or 10 mg of rivaroxaban or with 100 mg aspirin daily; however, compared with those receiving 10-mg rivaroxaban or aspirin, the women treated with 20-mg rivaroxaban more frequently had an increased menstrual flow duration and intensity. In our study, although more than half of the patients treated with DOACs received rivaroxaban, we could not evaluate the effects of 10-mg rivaroxaban as the few treated with low dose of the drug received 15-mg once a day (OID). Furthermore, in our study, the use of antiplatelet drugs (mostly aspirin 100 mg per day) was similar in women and in men and only at univariate but not at multivariate analysis resulted as a significant factor for bleeding. Altogether, our results seem not to confirm a higher risk of uterine bleeding with DOAC use. Only 11 vaginal bleeds were reported in all the investigated women (0.8%), 10 of which were in females of reproductive age. Although the difference was not statistically significant, seven events (4.8%, 2 were CRNMB) occurred in subjects treated with warfarin and only three (2.0%) in those receiving rivaroxaban. We conclude that the risk of uterine bleeding during DOACs treatment in VTE patients is very low, and similar – if not inferior – to that of warfarin use.

A relevant finding of this study was that more females than men had an impairment of the renal function. We mainly attribute this finding to the older age of included women who were significantly older than men. In fact, not only the median age was significantly higher in women (72 years) than in men (65 years) but also females were more prevalent than men in the upper age class (≥ 75 years: 43% versus 26.9%, respectively). Although the difference in age may well explain the more women with renal problems, we cannot exclude, in principle, that the participating clinical centers have done a selection of female patients with an impaired renal function to be included in the registry. It should be noticed, however, that despite the higher presence of renal diseases, usually reported as factor associated with a higher

risk of bleeding during anticoagulation treatment, the rate of MB and CRNMB bleeding was not higher in women than in men.

An interesting result of the present study is the significantly higher prevalence of isolated PE as index event in women than in men; furthermore, half of women aged ≤ 50 years with an isolated PE had the event in association with HC. These findings agree with our previous results in different cohorts of patients. In the DULCIS cohort,²⁵ 26.8% of the patients had isolated PE as the index event; this was more prevalent in females (34.1%) than in males (21.1%; $p < 0.0001$) and was especially prevalent in young females (aged ≤ 50 years) with an index event occurring during HC. Similar results were recorded in a subsequent different cohort of patients.²⁶ Altogether, these results suggest that the VTE presentation as isolated PE is somehow different than that as DVT/PE, with probably different pathogenic mechanisms which more frequently affect young women. Further studies are necessary to assess the underlying pathogenic mechanisms of this phenomenon, and in particular, the potential role of HC or other factors.

This study has limitations and strengths. It is an observational study, and the treatments used were left to the decision of attending physicians, without any indication by the study protocol. Another potential limitation is that the observation period of investigated patients was in average limited (median follow-up of less than 1 year). Finally, during the study observation period, either VKAs or DOACs were used for long-term VTE treatment; however, use of DOACs for this indication was still only a recent occurrence in Italy at that time. It is likely that some therapeutic decisions would be different today, with a larger use of low-dose regimens in DOAC-treated patients. Strength of the study is the multicentric design with a prospective collection of the patient data, together with accuracy and completeness of follow-up for all patients enrolled.

In conclusion, this study examined a similar number of female and male VTE patients included in a clinical registry since initiation of anticoagulation treatment (similarly performed with warfarin or DOACs) and prospectively followed-up during treatment. Women were in average older than men, with more frequent renal diseases, and with an index event that was more often associated

with weak RFs (mainly HC and pregnancy). The occurrence of MB or CRNMB during treatment was higher in women than in men only after inclusion of vaginal bleeds. The incidence of all bleeds was higher in women treated with warfarin and more vaginal bleeds (difference not statistically significant) occurred during warfarin than DOAC treatment.

Author contributions

GP conceived the study and wrote the first draft of the paper; CL performed the data analysis and contributed to the final version of the manuscript; EA monitored the data collection, contributed to data analysis and to the final version of the manuscript; BC, AF, DP, DM, VP, WA and ST collected the data and reviewed the manuscript; START 2-Register Investigators collected the data and their contributions are acknowledged.

Conflict of interest statement

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ORCID iD

Gualtiero Palareti  <https://orcid.org/0000-0002-4327-9561>

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List of participant Centers

The following Investigators and Centers participated to the START2-Register and contributed to the present study

- Walter Ageno, Giovanna Colombo, Dipartimento di Emergenza e Accettazione, Centro Trombosi ed Emostasi, Ospedale di Circolo, Università dell'Insubria, Varese
- Doris Barcellona, Struttura Dipartimentale di Emostasi e Trombosi, AOU di Cagliari, Dipartimento di Scienze Mediche e Sanità Pubblica, Università di Cagliari, Cagliari
- Barbara Bresciani, Cardiologia, Ospedale di Bentivoglio ASL Bologna, Bologna
- Eugenio Bucherini, Struttura Semplice Dipartimentale, Medicina Vascolare- Angiologia, Ospedale Civile Faenza, Faenza (RA)
- Paola Casasco, Centro diagnosi trombosi e sorveglianza terapia anticoagulanti, Immunoematologia Trasfusionale, Ospedale SS Antonio e Margherita, Tortona (AL)
- Paolo Chiarugi, Ambulatorio Antitrombosi per la sorveglianza dei pazienti in terapia anticoagulante orale, U.O. Analisi Chimico-Cliniche, Azienda Ospedaliero Universitaria Pisana, Pisa
- Antonio Chistolini, Alessandra Serrao, Sezione Ematologia, Dipartimento di Biotechnologie Cellulari ed Ematologia, Azienda Ospedaliero Universitaria Policlinico Umberto I, Roma
- Benilde Cosmi, UO Angiologia e Malattie della Coagulazione, Azienda Ospedaliero Universitaria di Bologna, Policlinico S. Orsola - Malpighi, Bologna
- Valeria De Micheli, Centro Emostasi e Trombosi, Ospedale di Lecco, Lecco
- Marcello Di Nisio, Medicina Vascolare e Malattie Trombemboliche, Ospedale SS.ma Annunziata, Pescara
- Rita Duce, S.C. Laboratorio di analisi, E.O. Ospedali Galliera, Genova
- Anna Falanga, Teresa Lerede, Luca Barcella, USC SIMT, Centro Emostasi e Trombosi, Ospedale Papa Giovanni XXIII, Bergamo

- Elvira Grandone, Donatella Colaizzo, Centro Trombosi Casa del Sollievo e della Sofferenza, S. Giovanni Rotondo (Foggia)
- Antonio Insana, Laboratorio Analisi, Ospedale Mauriziano, Torino
- Giuseppe Malcangi, Centro Emofilia e Trombosi, Policlinico di Bari, Bari
- Catello Mangione, Trasmusione, Ospedale di Galatina, Galatina (LE)
- Giuliana Martini, Centro Emostasi, Spedali Civili Di Brescia, Brescia
- Lucilla Masciocco, Pasquale Saracino, Centro Controllo Coagulazione, Dipartimento di Medicina-Geriatria-Lungodegenza, Policlinico Riuniti-Foggia, Presidio Ospedaliero Lastaria, Lucera (Foggia)
- Daniela Mastroiacovo, Dipartimento di Angiologia, Ospedale SS. Filippo e Nicola, Avezzano (L'Aquila)
- Marco Marzolo, UOC Medicina Interna, Ospedale di Rovigo, Rovigo
- Vincenzo Oriana, Centro Emofilia, Servizio Emostasi e Trombosi, Azienda Bianchi Melacrino Morelli, Reggio Calabria
- Carmelo Paparo, Patologia Clinica, Ospedale Maggiore, Chieri (Torino)
- Simona Pedrini, Federica Bertola, Servizio di Laboratorio, Istituto Ospedaliero Fondazione Poliambulanza Brescia, Brescia
- Vittorio Pengo, Gentian Denas, Elisa Bison, Dipartimento di Scienze Cardio-Toraco-Vascolari, Centro Trombosi, AOU Padova, Padova
- Antonietta Piana, Francesco Cibecchini, Centro Prevenzione e Cura Malattie Tromboemboliche Azienda Ospedaliera Universitaria San Martino-IST, Genova
- Pasquale Pignatelli, Daniele Pastori, Centro Trombosi, Clinica Medica Policlinico Umberto I°, Roma
- Daniela Poli, Rossella Marcucci, Niccolò Maggini, SOD Malattie Aterotrombotiche, Azienda Ospedaliera Universitaria-Careggi, Firenze
- Angelo Porfidia, UOC Medicina Generale, Policlinico Universitario Gemelli, Roma
- Serena Rupoli, Clinica Ematologica, Ospedali Riuniti Ancona, Ancona
- Domizio Serra, Centro Trombosi, Ospedale Evangelico Internazionale, Genova
- Sophie Testa, Oriana Paoletti, Centro Emostasi e Trombosi, Laboratorio Analisi chimico-cliniche e microbiologiche, Azienda Socio Sanitaria Territoriale di Cremona, Cremona
- Andrea Toma, Pietro Barbera, UOC di Patologia Clinica, Ambulatorio Terapia Anticoagulante Orale, O.C. "L.Cazzavillan", Arzignano (Vicenza)
- Alberto Tosetto, Divisione di Ematologia, Ospedale San Bortolo, Vicenza
- Claudio Vasselli, Laboratorio Patologia Clinica, Policlinico Casilino, Roma
- Adriana Visonà, UOC Angiologia, Ospedale San Giacomo Apostolo, Castelfranco Veneto (Treviso)
- Maddalena Loredana Zighetti, SIMT- AO San Paolo, Milano

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