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Original Article

Sex differences in venous thromboembolism outcomes: findings from the GARFIELD-VTE registry

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ABSTRACT

Background: The association of sex with clinical outcome risk in venous thromboembolism (VTE) is unclear.
Objective: To investigate sex differences in clinical outcomes and anticoagulation effectiveness in VTE in the GARFIELD-VTE registry.
Methods: Outcomes included all-cause mortality, VTE recurrence, major and any bleeding, myocardial infarction (MI)/acute coronary syndrome (ACS), and stroke/transient ischaemic attack (TIA) over 3 years of follow-up. Hazard ratios were calculated using Cox proportional hazard models with an assessment of sex interactions with parenteral, vitamin K antagonist (VKA), and direct oral anticoagulant (DOAC) therapies.
Results: Of 10,650 patients, 5290 (49.7%) were female and 5360 were male. Females and males had comparable ages (median [Q1-Q3]; females: 60.6 [44.0–72.9] years, males: 60.0 [48.0–70.3] years), body mass index (females: 27.6 [23.6–32.7] kg/m^2, males: 27.1 [24.4–30.6] kg/m^2), and anticoagulant treatment. Females had greater risk of major (adjusted hazard ratio [95% CI (1.25 [1.01–1.55]) and any bleeding (1.32 [1.18–1.47]) than males, but lower risk of recurrent VTE (0.82 [0.72; 0.94]), MI/ACS (0.52 [0.36–0.76]) and stroke/TIA (0.72 [0.52–0.99]). VKA-treated females had greater risk of major (1.69 [1.16–2.48]) and any bleeding (1.43 [1.18–1.73]) than VKA-treated males, while DOAC-treated females had greater risk of any bleeding (1.37 [1.17–1.61]) but not major bleeding (1.22 [0.86–1.72]) than DOAC-treated males. Sensitivity analyses excluding patients with active cancer (N = 9752) yielded similar results.

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Conclusions: Compared with males, females with VTE have a greater risk of bleeding, but a lower risk of recurrent VTE, MI/ACS, and stroke/TIA. Sex appears to affect the relationship between VKA and DOAC treatment and bleeding in VTE.

1. Introduction

Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), is a major cause of morbidity and mortality [1] VTE is linked to several risk factors, including age, obesity, immobilisation, and active cancer [2] VTE is also associated with biological sex, with epidemiological data showing males and females have different susceptibility to VTE at different life stages [3–7] Furthermore, the risk of hospitalisation due to VTE and the length of hospital stay are influenced by sex [8,9]

The impact of sex on clinical outcomes after VTE diagnosis is unclear. Some studies have suggested that females anticoagulated for VTE have a higher risk of major bleeding than males [10–12] In contrast, other studies have found no association between sex and bleeding risk [13–15] Likewise, some VTE registry data indicate no sex differences in VTE recurrence [13,14] However, analyses of other clinical cohorts and randomised trials have found that the male sex is associated with a significantly higher risk of VTE recurrence [16–19]

Given these conflicting data, there is a need to re-examine the impact of sex on clinical outcomes after VTE diagnosis. Moreover, clarity is required on the time course of clinical outcome susceptibility in each sex and whether anticoagulation treatments are similarly effective at improving outcomes in male and female patients. This study used data from The Global Anticoagulant Registry in the Field-Venous Thromboembolism (GARFIELD-VTE) registry to examine the association of sex with 3-year clinical outcome risk in VTE patients and to assess the effectiveness and potential difference in effects by sex of baseline anticoagulation treatment on these outcomes.

2. Methods

2.1. Study design and participants

GARFIELD-VTE (NCT02155491) is an international, non-interventional, prospective, observational registry designed to represent the real-world incidence and management of acute VTE [20] Men and women ≥18 years diagnosed with VTE within 30 days of entry into the registry were included. Registry enrolment occurred between May 2014 and January 2017 at 418 sites in 28 countries. Patients with recurrent VTE must have completed treatment for the previous VTE episode. Those with superficial vein thrombosis, participants in an interventional study, or those with missing or inconsistent endpoint records were excluded. VTE patients were managed according to local practices. Decisions to initiate, continue, or change treatment were at the discretion of the treating physicians and their patients.

2.2. Selection of study sites

The national coordinating investigator identified the care settings most representative of VTE management in their country. The contract research organisation provided a list of sites that reflected these care settings, before contacting a random sample from the list. Sites that agreed to participate were recruited after a qualification telephone call. The investigator was required to complete a program providing guidance on patient screening, enrolment, and follow-up in the registry.

2.3. Data source

Patient data were collected using an electronic case report form (eCRF) submitted to the coordinating centre (Thrombosis Research Institute, London, UK). The coordinating centre was responsible for ensuring the completeness and accuracy of data collection. The registry protocol mandated that 10 % of all eCRFs were verified with source documentation, that electronic audit trails were available for all data modifications, and that critical variables were subjected to additional audits. The data were extracted from the study database on October 14, 2020.

2.4. Ethics statement

The registry was conducted in accordance with the Declaration of Helsinki and guidelines from the International Conference on Harmonisation on Good Clinical Practice (GCP) and Good Pharmacoepidemiological Practice (GPP). The registry protocol was approved by independent ethics committee for each participating country and the hospital-based institutional review board. All patients provided written informed consent to participate. Confidentiality and anonymity of patients were maintained.

2.5. Clinical outcomes

The primary outcomes were all-cause mortality, recurrent VTE, major bleeding, any bleeding, myocardial infarction (MI)/acute coronary syndrome (ACS), and stroke/transient ischaemic attack (TIA). We also assessed the interaction for the primary outcomes between sex and the following anticoagulation treatments: parenteral therapy, vitamin K antagonist (VKA) therapy, and direct oral anticoagulation (DOAC) therapy.

2.6. Definitions

Recurrent VTE was defined as a confirmed diagnosis of VTE after completion of treatment for a prior VTE event. Major bleeding was defined as clinically overt bleeding at a critical site, a decrease in haemoglobin (≥2 g/dL), transfusion of ≥2 units of packed red blood cells, or a fatal bleed [21] Non-major bleeding was defined as overt bleeding that did not meet the criteria for major bleeding. Patients diagnosed with or treated for cancer ≤90 days before VTE diagnosis or ≤30 days after VTE diagnosis were classified as having active cancer. History of cancer was defined by the patient being in remission or having not received cancer treatment within 90 days before VTE diagnosis. Renal insufficiency was defined as stage III-V chronic kidney disease in patients with a glomerular filtration rate of <60 mL/min/1.73 m^2 calculated with an equation from the Modification of Diet in Renal Disease study [22]

2.7. Statistical analyses

Continuous data were presented as median values with first and third quartiles. Categorical data were presented as frequency and percentage. Primary outcome event rates at 3-year follow-up were calculated per 100 person-years with the 95% confidence interval (CI) using Poisson regression. Time-to-event analyses of clinical outcomes were performed with Cox proportional hazards models and reported as hazard ratios (HRs) and their corresponding 95% CIs. Analyses were conducted both unadjusted and adjusted for the following covariates: age, ethnicity, body mass index (BMI), recent bleeding/anaemia, chronic heart failure, chronic immobilisation, active cancer, thrombophilia, prior VTE event, renal insufficiency, and treatment type. Differences in clinical outcomes were also examined using cumulative incidence curves considering all-cause mortality as a competing risk. The interactions of sex with OAC

therapies were added to explore potential differences in treatment effects for females versus males.

Patients were assumed to have consistent adherence to therapy type from baseline until treatment completion or discontinuation. Discontinuation for ≥7 days was considered permanent discontinuation of treatment. Interactions of sex by treatment (VKA, DOAC, or parenteral only) on clinical outcomes were also assessed using Cox proportional hazard models. Two sensitivity analyses were performed; the interaction model of all outcomes was repeated following the exclusion of patients with active cancer and the interaction model of bleeding was repeated after exclusion of female-specific bleeds. A secondary analysis was also conducted that observed the rate of recurrent VTE in patients with unprovoked VTE after discontinuing anticoagulation. This was determined using adjusted and unadjusted Cox proportional hazards models as above, but with time zero as time at anticoagulant discontinuation. For the multivariable models, there were some missing data in the age, BMI, and anticoagulation variables, which were treated using multiple imputations. Analyses were performed using SAS® Enterprise Guide version 8.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient characteristics and baseline treatment patterns

Of the 10,864 patients enrolled in the registry (**Figure S1**), after exclusion of 185 patients with unconfirmed VTE and 29 with inconsistent data reporting, a total of 10,650 were included in the analysis (5360 males and 5290 females).

Baseline patient characteristics are shown in Table 1. Male and female patients had similar median age and BMI. The proportion of current smokers was greater in males (22.4%) than females (9.6%). The proportions of care setting and care specialty types at VTE diagnosis were similar between males and females. The median creatinine clearance rates and haemoglobin levels in male and female patients were within the expected levels, with males having slightly higher values. The median platelet levels were also similar between male and female patients, as were the international normalised ratios. The relative proportions of patients with primary diagnosis of DVT, PE, or DVT and PE were similar, as was the site of DVT, the balance of unilateral and bilateral DVT, and the type of lower limb DVT. Male and female patients had comparable baseline prescription rates for lone parenteral, VKA, or DOAC therapies, as well as combinations of parenteral agents with VKAs or DOACs.

Table 1
Baseline patient characteristics.

Covariate	Male $N = 5360$	Female $N = 5290$
Age, median (Q1; Q3)	60.0 (48.0;70.3)	60.6 (44.0;72.9)
BMI, median (Q1; Q3)	27.1 (24.4;30.6)	27.6 (23.6;32.7)
Ethnicity *n* (%)		
Asian	851 (16.8)	1109 (22.3)
Black	177 (3.5)	292 (5.9)
Caucasian	3706 (73.2)	3223 (64.8)
Multi-racial	25 (0.5)	31 (0.6)
Unwilling to declare/other/ unknown	302 (6.0)	317 (6.4)
Smoking status *n* (%)		
Never smoker	2310 (44.9)	3989 (78.1)
Ex-smoker	1683 (32.7)	627 (12.3)
Current smoker	1151 (22.4)	493 (9.6)
Region *n* (%)		
Europe	3201 (59.7)	2779 (52.5)
Asia	771 (14.4)	1041 (19.7)
North America/Australia	759 (14.2)	676 (12.8)
Latin America	162 (3.0)	218 (4.1)
Africa/Middle East	467 (8.7)	576 (10.9)
Care setting *n* (%)		
Hospital	3934 (73.4)	3863 (73.0)
Outpatient	1426 (26.6)	1427 (27.0)
Care specialty *n* (%)		
Vascular medicine	2413 (45.0)	2362 (44.7)
General practitioner	195 (3.6)	184 (3.5)
Internal medicine	2336 (43.6)	2280 (43.1)
Emergency medicine	140 (2.6)	135 (2.6)
Cardiology	273 (5.1)	327 (6.2)
Creatinine clearance, median Cockroft Gault (Q1; Q3)	97.9 (71.0;127.2)	87.2 (61.0;120.5)
Haemoglobin, median g/dL (Q1; Q3)	14.0 (12.4;15.0)	12.2 (10.9;13.5)
Platelets, Median 10^9/L (Q1; Q3)	220.0 (175.0;276.0)	244.0 (194.0;308.0)
INR* *n* (%)		
<1.5	3446 (85.8)	3360 (85.1)
1.5-<2.0	251 (6.3)	256 (6.5)
2.0–3.0	229 (5.7)	227 (5.7)
>3.0	89 (2.2)	105 (2.7)
Primary diagnosis *n* (%)		
Deep Vein Thrombosis (DVT)	3291 (61.4)	3277 (61.9)
Pulmonary Embolism (PE)	1174 (21.9)	1274 (24.1)
DVT and PE	895 (16.7)	739 (14.0)
Site of DVT *n* (%)		
Upper limb	239 (5.7)	195 (4.8)
Lower limb	3869 (92.6)	3742 (93.3)
Cava vein (inferior)	47 (1.1)	53 (1.3)
Cava vein (superior)	25 (0.6)	24 (0.6)
Site of DVT: unilateral or bilateral *n* (%)		
Left	2153 (51.5)	2221 (55.3)
Right	1761 (42.2)	1509 (37.6)
Both	262 (6.3)	282 (7.0)
Type lower limb DVT *n* (%)		
Distal	1295 (33.9)	1368 (36.9)
Proximal	1407 (36.8)	1368 (36.9)
Both Distal and Proximal	1120 (29.2)	974 (26.3)
Baseline treatment *n* (%)		
Parenteral therapy only	817 (15.4)	971 (18.7)
VKA only	301 (5.7)	316 (6.1)
DOAC only	1698 (32.1)	1620 (31.1)
Parenteral therapy + VKA	1442 (27.2)	1317 (25.3)
Parenteral therapy + DOAC	895 (16.9)	818 (15.7)
Other AC	47 (0.9)	63 (1.2)
No AC treatment	93 (1.8)	96 (1.8)

*Only applicable to patients treated with VKA therapy. BMI: body mass index, INR: international normalized ratio, VKA: vitamin K antagonist, DOAC: direct oral anticoagulant, AC: anticoagulant.

3.2. Risk factors for VTE in male and female patients

In male and female patients, the most common risk factor for VTE was a prior episode of DVT or PE (Table 2). Female patients had a recent bleeding event or anaemia, experienced chronic immobilisation, or had a previous cancer diagnosis more commonly than male patients. Male patients had a slightly greater prevalence of renal insufficiency and prior episodes of DVT or PE.

3.3. Clinical outcomes after 3-year follow-up from VTE diagnosis

In the unadjusted analyses, female VTE patients had higher event rates of major bleeding and any bleeding than male patients (Table 3). Conversely, female patients had lower rates of recurrent VTE and MI/ACS. After adjustment for confounding factors, female patients had a lower risk of recurrent VTE (adjusted HR [95% CI]; 0.82 [0.72; 0.94]), MI/ACS (0.52 [0.36; 0.76]), and stroke/TIA (0.72 [0.52; 0.99]) compared with male patients (Fig. 1). Females had a greater risk of major bleeding (1.25 [1.01; 1.55]) and any bleeding (1.32 [1.18; 1.47]) than males. The causes of major bleeding and minor bleeding were similar between male and female patients, as were the distribution of bleeding sites, except for female-specific sites (metrorrhagia and menorrhagia, **Table S1**). In a sensitivity analysis with exclusion of female-specific sites, there were no differences in the rates or adjusted 3-year risk of major or any bleeding between female and male patients (**Table S2**).

Table 2
Baseline provoked and unprovoked venous thromboembolism risk factors.

Risk factor*	Male $N = 5360$	Female $N = 5290$
Acute medical illness	300 (5.6)	305 (5.8)
Hospitalisation	620 (11.6)	672 (12.7)
Long-haul travelling	282 (5.3)	243 (4.6)
Trauma of the lower limb	439 (8.2)	388 (7.3)
Surgery	643 (12.0)	683 (12.9)
Active cancer	425 (7.9)	473 (8.9)
Pregnancy	0 (0.0)	192 (3.6)
Recent bleed or anaemia	126 (2.4)	244 (4.6)
Chronic heart failure	171 (3.2)	164 (3.1)
Chronic immobilisation	254 (4.7)	355 (6.7)
Family history of VTE (first degree relatives)	318 (5.9)	330 (6.2)
History of cancer	552 (10.3)	629 (11.9)
Known thrombophilia	159 (3.0)	156 (2.9)
Oral contraception	0 (0.0)	529 (10.0)
Prior episode of DVT and/or PE	881 (16.4)	732 (13.8)
Renal insufficiency	224 (4.2)	163 (3.1)

*Not mutually exclusive categories. VTE: venous thromboembolism, DVT: deep vein thrombosis, PE: pulmonary embolism.

Table 3
Event rates of clinical outcomes stratified by sex.

Outcome	Sex	No. of events	Rate (95% CI)
All-cause mortality	Female	591	4.54 (4.19, 4.92)
	Male	568	4.27 (3.93, 4.64)
Recurrent VTE	Female	568	3.74 (3.41, 4.09)
	Male	470	4.27 (3.93, 4.64)
Major bleeding	Female	208	1.64 (1.43, 1.88)
	Male	155	1.18 (1.01, 1.38)
Any bleeding	Female	758	6.57 (6.11, 7.05)
	Male	583	4.73 (4.37, 5.14)
MI/ACS	Female	46	0.36 (0.27, 0.47)
	Male	83	0.63 (0.51, 0.78)
Stroke/TIA	Female	67	0.52 (0.41, 0.66)
	Male	91	0.69 (0.56, 0.85)

Event rates are per 100 person-years, presented with 95% confidence interval (CI). VTE: venous thromboembolism, MI: myocardial infarction, ACS: acute coronary syndrome, TIA: transient ischaemic attack.

3.4. Time to primary outcome event analysis across 3-year follow-up

Fig. 2 shows the cumulative incidences of clinical outcomes over three years in female and male VTE patients. There was no sex-based difference during the first year for MI/ACS and the first two years for recurrent VTE and stroke/TIA. A greater incidence in males appeared in the later follow-up periods (Fig. 2**a,** 2**d,** 2**e**). In contrast, 30 days after enrolment, approximately 0.9% of female patients and 0.4% of male patients had a major bleeding event, which increased in disparity until the end of follow-up (3.8% in females, 2.3% in males) (Fig. 2**b**). A similar trend was seen in the combination of any bleeding event, with a cumulative incidence in female patients at 30, 90, and 180 days, and 1, 2, and 3 years of 3.4%, 6.6%, 9.0%, 11.4%, 11.6%, and 14.7%, respectively (Fig. 2**c**).

3.5. Interaction of sex with anticoagulation therapy in VTE

Female VTE patients who received parenteral anticoagulation treatment were less likely to have a recurrent VTE (adjusted HR [95% CI]; 0.69 [0.50; 0.95]) or a MI/ACS event (0.36 [0.14; 0.89]) than male patients on the same treatment (Fig. 3). The difference in risks for females versus males varied little when treated with VKA versus DOAC therapies for the outcomes of any bleeding and MI/ACS (interaction p-values = 0.75 and 0.90, respectively). Compared with males on the same treatment, female patients treated with VKA therapy had a greater risk of major bleeding (1.69 [1.16; 2.48]). Similarly, female patients treated with VKA (1.43 [1.18; 1.73]) or DOAC therapy (1.37 [1.17; 1.61]) had a greater risk of any bleeding than males on the same treatment. A significant interaction was found for major and any bleeding outcomes when comparing the difference in sex-based risks for VKA versus parenteral anticoagulants (interaction $p = 0.023$, 0.026, respectively). There was no difference in females versus males who received parenteral therapy (major bleeding: 0.90 [0.60; 1.33], any bleeding: 0.99 [0.76; 1.29]). However, no differences in bleeding risk for females versus males remained once female-specific bleeding sites were excluded (**Table S3**).

In another sensitivity analysis excluding patients with active cancer ($N = 9752$), the greater risks of major bleeding and any bleeding in females treated with VKA were maintained, as was the reduced risk of

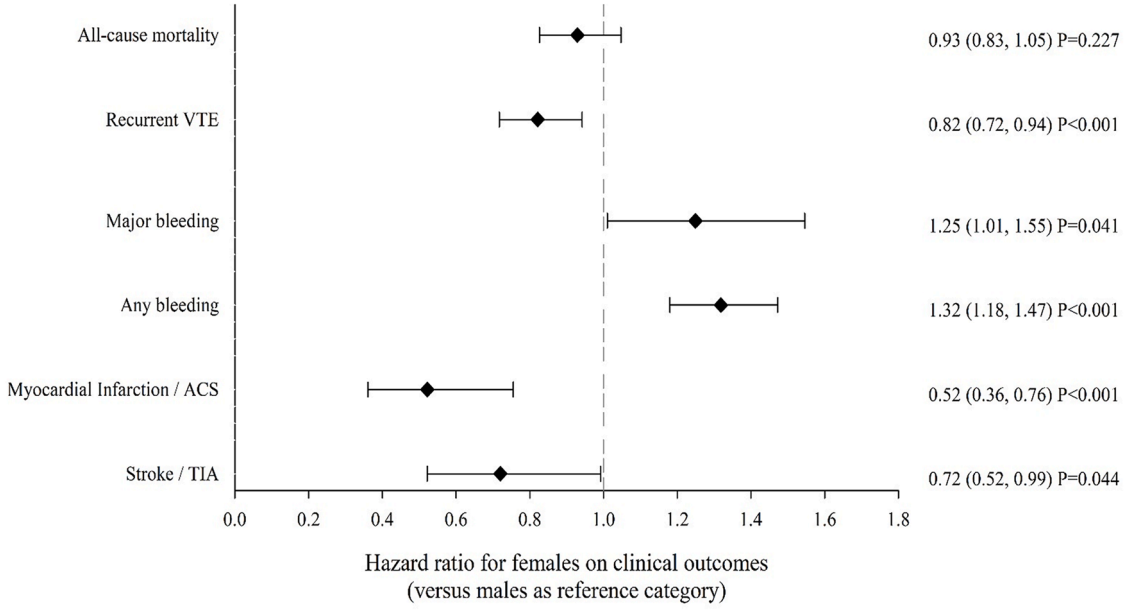

Fig. 1. Clinical outcome risks in female venous thromboembolism (VTE) patients relative to male patients. Results are shown as forest plots with adjusted hazard ratio and 95% confidence interval for each outcome after 3-year follow-up from VTE diagnosis. Values greater than one indicate an increase of the hazard rate of females over males (reference group). Hazard ratios were adjusted for age, ethnicity, body mass index, recent bleeding/anaemia, chronic heart failure, chronic immobilisation, active cancer, thrombophilia, prior VTE event, renal insufficiency, and treatment type. ACS: acute coronary syndrome; TIA, transient ischemic attack.

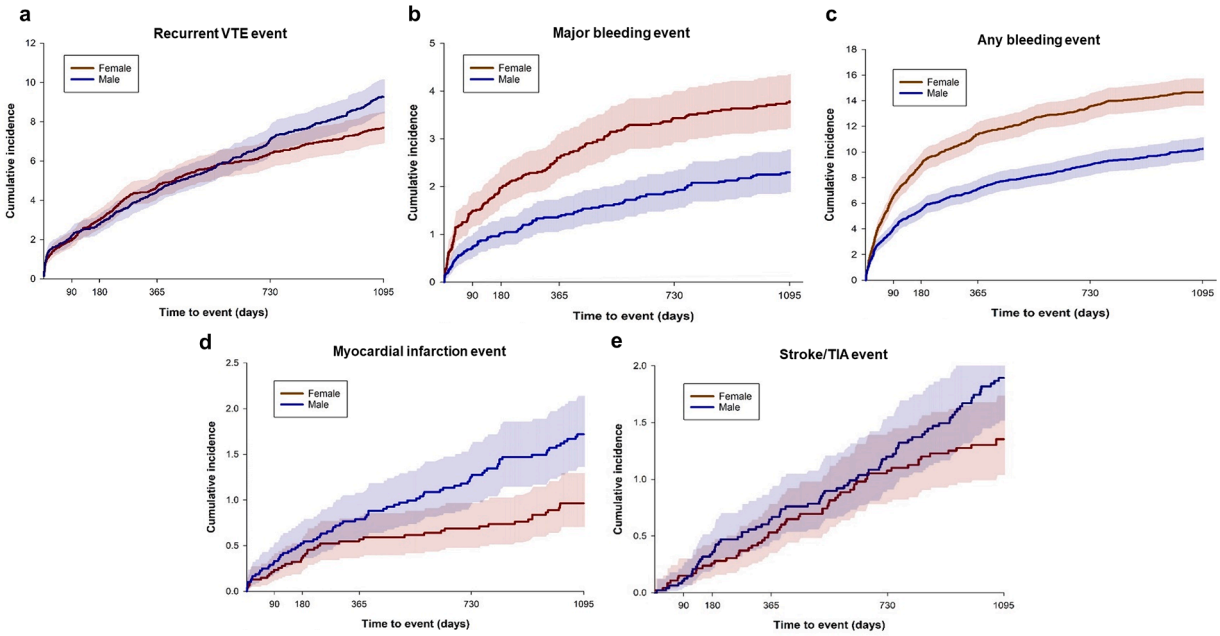

Fig. 2. Cumulative incidence of male and female venous thromboembolism (VTE) patients with a clinical outcome with mortality as a competing risk throughout 3-year follow-up. Data are presented as cumulative incidence curves stratified by female (red) and male (blue) patients with follow-up time on the x-axes (in days) for recurrent VTE (a), major bleeding (b), any bleeding (c), myocardial infarction (d), and stroke/transient ischaemic attack (TIA) (e).

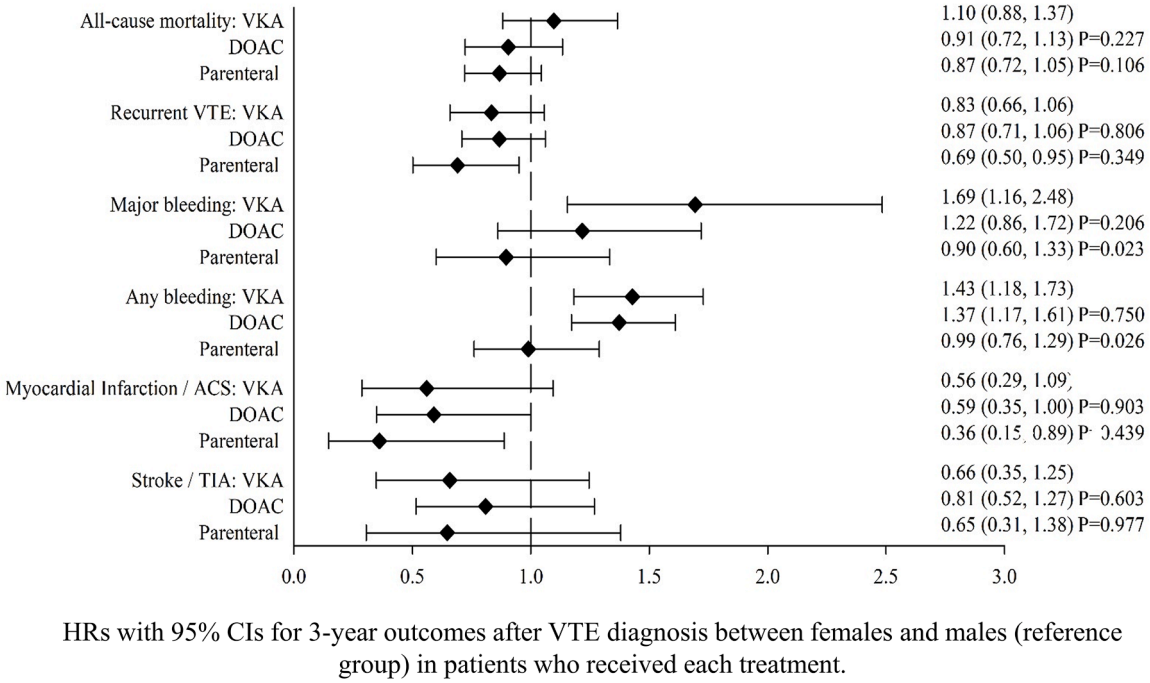

Fig. 3. Clinical outcome risks in female venous thromboembolism (VTE) patients relative to male patients according to baseline anticoagulation treatment type. Results are shown as forest plots with the adjusted hazard ratio (HR) and 95% confidence interval (CI) for each outcome and treatment type after 3-year follow-up from VTE diagnosis. Values greater than one indicate an increase of the hazard rate of females over males (reference group) on the same anticoagulation treatment. Hazard ratios were adjusted for age, ethnicity, body mass index recent bleeding/anaemia, chronic heart failure, chronic immobilisation, active cancer, thrombophilia, prior VTE event, and renal insufficiency. P-values express the interaction of sex with VKA versus either DOAC or parenteral therapy. VKA: vitamin K antagonist, DOAC: direct oral anticoagulant, ACS: acute coronary syndrome; TIA, transient ischemic attack.

MI/ACS in female patients treated with a parenteral anticoagulant (**Table S4**).

3.6. Unprovoked VTE

In patients with an unprovoked index VTE episode ($N = 4068$), the incidence of VTE recurrence after anticoagulant discontinuation was not significantly different between male and female patients (events per 100-person years; males: 4.64 [3.73; 5.78] vs. females: 4.73 [3.78; 5.94]). Additionally, the unadjusted and adjusted risk of VTE recurrence after anticoagulant discontinuation was not different in females and males (unadjusted HR: 0.99 [0.72; 1.36]; adjusted HR: 1.02 [0.74;

1.31]).

4. Discussion

We found that female VTE patients have a greater risk of major and any severity bleeding than male patients, but a reduced risk of recurrent VTE, MI/ACS, and stroke/TIA. These differential risks were evident at all stages of follow-up and were independent of VTE risk factors and anticoagulation treatment, except the use of parenteral therapy and bleeding. Of interest, female VTE patients who received VKA therapy had a greater risk of major bleeding than male patients on the same treatment, while the association became nonsignificant between sex and major bleeding for patients on DOACs and significantly different with parenteral therapy. These findings suggest that biological sex influences the susceptibility to clinical outcomes and the effectiveness of anticoagulation therapies in VTE patients.

4.1. Bleeding risk is greater in female VTE patients

By the end of the 3-year follow-up, 3.9 % of female VTE patients experienced a major bleeding event, which was lower than the 9.2 % rate from the Japanese COMMAND VTE registry and 12% from American Worcester VTE study [14,23] Despite the relatively low incidence, major bleeding occurred more frequently in female patients than male patients, with the disparity emerging within 30-60 days and widening throughout the follow-up. Adjusted hazard models showed female patients had a 25% greater risk of major bleeding over 3 years, consistent with meta-analyses indicating a 20-37% increased risk for females with VTE [11,12,15] This contrasts with the non-significant sex difference in bleeding risk in the Japanese COMMAND VTE registry [14] However, the sex-based difference in bleeding is dependent on inclusion of female-specific metrorrhagia and menorrhagia; removal of female-specific bleeding sites made the association non-significant. This is consistent with the Italian START-Register, which only found a significant sex-based difference in bleeding when vaginal/uterine sites were included in analysis [24] In our view, this secondary finding does not detract from the finding of the main analysis that females with VTE have greater bleeding risk. By ignoring female-specific bleeding, we would fail to capture the bleeding risks in real-world female VTE patients. Instead, our findings suggest that approaches that mitigate bleeding at female-specific sites while also providing anticoagulation should be used in female VTE patients.

4.2. Sex differences in VTE recurrence

Sex has been inconsistently associated with VTE recurrence. Meta-analyses of randomised trials show no difference between females and males [11,12] However, a meta-analysis inclusive of cohort studies and randomised trials suggests that males have a 1.8-fold greater risk [16] Our real-world data aligns with the latter, with male patients having a nearly 20% greater VTE recurrence risk over the 3-year follow-up than female patients [25] Interestingly, males had a greater risk of VTE recurrence despite having an overall lower prevalence of persistent VTE-provoking risk factors compared with females. This might suggest that male VTE patients are inherently more susceptible to VTE recurrence than female patients. However, when our analysis was limited to patients with an unprovoked index VTE event who had stopped anticoagulant therapy, there was no difference in VTE recurrence risk. This contrasts with a 2.8-fold greater risk of VTE recurrence in males with an unprovoked index VTE event than in females in the Leiden Thrombophilia study [17]; although this population was considerably younger, had a longer median follow-up period than our study, and women on hormonal treatment were not excluded.

Taken together, our findings support the inclusion of sex in VTE recurrence risk stratification, as proposed by the sex-specific AIM-SHARP VTE recurrence scores [26], while also providing a rationale for further pre-clinical and clinical research into the inherent VTE recurrence risks in male and female VTE patients. Given the lower VTE recurrence risk but higher bleeding risk in females, our findings also establish rationale for further research into the role of sex in anticoagulant decision making, including whether males and females are better suited to certain anticoagulant types, anticoagulant doses, or short- and long-term treatment durations.

4.3. Female VTE patients have a lower risk of MI and stroke

In addition to sex differences in bleeding and VTE recurrence, we found that female patients have a nearly 50% lower risk of MI/ACS risk and a 28% lower risk of stroke/TIA. Limited research exists on sex differences in MI and stroke risk among VTE patients. One study from Taiwan found males with unprovoked VTE had a 35% higher risk of adverse cardiovascular events, including ACS and stroke [27]. Another study reported that VTE increases the MI and stroke risk in female patients over 65, but not in males [28]. This suggests that sex influences MI and stroke risk, though not entirely consistent with our results. Further research is needed to clarify sex-related risks for arterial thrombotic events, especially in ageing VTE patients. Nonetheless, our findings indicate sex differences in MI and stroke, as well as bleeding and VTE recurrence, in a real-world VTE patient population.

4.4. Sex-based differences in outcome risk on anticoagulation therapies

The collation of data from randomised trials suggests that a patient's sex affects the association of edoxaban with bleeding risk [11]. Similarly, we show here that VKA-treated female patients have a nearly 70% greater risk of major bleeding than VKA-treated male patients. Only female patients on parenteral therapy, and not those on VKA or DOAC therapy, were afforded protection against recurrent VTE or MI/ACS when compared with males on the same therapy. This suggests that sex might be a determinant of the effectiveness of anticoagulant therapy. By extension, it suggests that sex should inform anticoagulation therapy decision-making. Further research in the form of a randomised trial or appropriately weighted comparative effectiveness observational study is required to appropriately evaluate the effect of sex on specific DOAC types for VTE management.

4.5. Limitations

Our study has several limitations. Firstly, we analysed data from an observational registry where the attending clinicians decided on patient enrolment and on VTE management, introducing potential selection bias. In particular, patients enrolled in the registry have been more likely to receive a novel anticoagulant, such as a DOAC, rather than older therapies like VKAs or parenteral agents. Secondly, we did not stratify patients according to DOAC type because rivaroxaban made up over 75% of DOAC prescriptions in GARFIELD-VTE [29]. Therefore, we cannot discount whether the results of our study are due to the differential effects of a specific DOAC therapy. Finally, we did not perform genetic profiling of our population. Hence, it is possible that the uneven distribution of genetic mutations known to be associated with sex-based outcomes in VTE, such as factor V Leiden or prothrombin 20210G-A mutations, influenced the results of our study [30]

5. Conclusion

Sex is associated with clinical outcomes in an international population of VTE patients. Female VTE patients have a greater risk of major bleeding from over 3 years of follow-up, with a parallel lower risk of recurrent VTE, MI/ACS, and stroke/TIA. Further research is required to determine why sex influences clinical outcomes in VTE patients and to determine how consideration of a patient's sex should guide VTE management.

Author Contributions

Conceptualization, Methodology, Supervision: P. Prandoni, M. Fluharty, K. Pieper, A. Kakkar. Data curation, Formal analysis, Visualization: P. Prandoni, M. Fluharty, K. Pieper. Investigation, Project administration: P. Prandoni, H. Bounameaux, S. Haas, L. Mantovani, S. Sholkamy, K. Kondo, H. Gibbs, Z-C. Jing, C-E Chiang, P. Verhamme, A. Turpie, J. Weitz, W. Ageno, S. Goto, P. Angchaisuksiri, A. Kakkar. Writing – original draft: P. Prandoni, M. Fluharty, H. Gibbs, J. Weitz, W. Ageno, K. Pieper, A. Kakkar. Writing – review and editing: All authors. All authors approved the final manuscript.

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Data availability

Aggregated data can be shared upon reasonable request and receipt of an analysis plan to Karen Pieper

Disclosure of conflict of interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2025.106492.

References

[1] Raskob GE, Angchaisuksiri P, Blanco AN, et al. Thrombosis: a major contributor to global disease burden. Arterioscler Thromb Vasc Biol 2014;34:2363–71.
[2] Ageno W, Becattini C, Brighton T, et al. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. Circulation 2008;117:93–102.
[3] Silverstein MD, Heit JA, Mohr DN, et al. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med 1998;158:585–93.
[4] Næss IA, Christiansen SC, Romundstad P, et al. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost 2007;5:692–9.
[5] Holst AG, Jensen G, Prescott E. Risk factors for venous thromboembolism: results from the Copenhagen City Heart Study. Circulation 2010;121:1896–903.
[6] Johansson M, Johansson L, Lind M. Incidence of venous thromboembolism in northern Sweden (VEINS): a population-based study. Thromb J 2014;12:1–7.
[7] Lind MM, Johansson M, Själander A, et al. Incidence and risk factors of venous thromboembolism in men and women. Thromb Res 2022;214:82–6.
[8] Marshall AL, Bartley AC, Ashrani AA, et al. Sex-based disparities in venous thromboembolism outcomes: a National Inpatient sample (NIS)-based analysis. Vasc Med 2017;22:121–7.
[9] Mansour S, Alotaibi G, Wu C, et al. Sex disparities in hospitalization and mortality rates for venous thromboembolism. J Thromb Thrombolys 2017;44:197–202.
[10] Dreijer AR, Diepstraten J, Brouwer R, et al. Risk of bleeding in hospitalized patients on anticoagulant therapy: prevalence and potential risk factors. Eur J Intern Med 2019;62:17–23.
[11] Loffredo L, Violi F, Perri L. Sex related differences in patients with acute venous thromboembolism treated with new oral anticoagulants. A meta-analysis of the interventional trials. Int J Cardiol 2016;212:255–8.
[12] Alotaibi GS, Almodaimegh H, McMurtry MS, et al. Do women bleed more than men when prescribed novel oral anticoagulants for venous thromboembolism? A sex-based meta-analysis. Thromb Res 2013;132:185–9.
[13] Giustozzi M, Valerio L, Agnelli G, et al. Sex-specific differences in the presentation, clinical course, and quality of life of patients with acute venous thromboembolism according to baseline risk factors. Insights from the PREFER in VTE. Eur J Intern Med 2021;88:43–51.
[14] Yoshikawa Y, Yamashita Y, Morimoto T, et al. Sex differences in clinical characteristics and outcomes of patients with venous thromboembolism–from the COMMAND VTE registry–. Circ J 2019;83:1581–9.
[15] Lapner ST, Cohen N, Kearon C. Influence of sex on risk of bleeding in anticoagulated patients: a systematic review and meta-analysis. J Thromb Haemost 2014;12:595–605.
[16] Douketis J, Tosetto A, Marcucci M, et al. Risk of recurrence after venous thromboembolism in men and women: patient level meta-analysis. Br Med J 2011; 342.
[17] Christiansen S, Lijfering W, Helmerhorst F, et al. Sex difference in risk of recurrent venous thrombosis and the risk profile for a second event. J Thromb Haemost 2010;8:2159–68.
[18] McRae S, Tran H, Schulman S, et al. Effect of patient's sex on risk of recurrent venous thromboembolism: a meta-analysis. Lancet 2006;368:371–8.
[19] Kyrle PA, Minar E, Bialonczyk C, et al. The risk of recurrent venous thromboembolism in men and women. N Engl J Med 2004;350:2558–63.
[20] Weitz JI, Haas S, Ageno W, et al. Global anticoagulant registry in the field–venous thromboembolism (GARFIELD-VTE). Thromb Haemost 2016;116:1172–9.
[21] Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692–4.
[22] Levey AS, Coresh J, Bolton K, et al. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kid Dis 2002;39. i-ii+ S1-S266.
[23] Spencer FA, Emery C, Joffe SW, et al. Incidence rates, clinical profile, and outcomes of patients with venous thromboembolism. The Worcester VTE study. J Thromb Thrombolys 2009;28:401–9.
[24] Palareti G, Legnani C, Antonucci E, et al. Do women with venous thromboembolism bleed more than men during anticoagulation? Data from the real-life, prospective START-Register. Ther Adv Drug Saf 2021;12: 20420986211062965.
[25] Kearon C, Ageno W, Cannegieter S, et al. Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. J Thromb Haemost 2016;14:1480–3.
[26] Albertsen IE, Søgaard M, Goldhaber SZ, et al. Development of sex-stratified prediction models for recurrent venous thromboembolism: a Danish nationwide cohort study. Thromb Haemost 2020;120:805–14.
[27] Chang WT, Chang CL, Ho CH, et al. Long-term effects of unprovoked venous thromboembolism on mortality and major cardiovascular events. J Am Heart Assoc 2017;6:e005466.
[28] Lind C, Flinterman LE, Enga KF, et al. Impact of incident venous thromboembolism on risk of arterial thrombotic diseases. Circulation 2014;129:855–63.
[29] Haas S, Ageno W, Weitz JI, et al. Anticoagulation therapy patterns for acute treatment of venous thromboembolism in GARFIELD-VTE patients. J Thromb Haemost 2019;17:1694–706.
[30] Tzoran I, Papadakis E, Brenner B, et al. Gender-related differences in the outcome of patients with venous thromboembolism and thrombophilia. Thromb Res 2017; 151:S11–5.