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The influence of anemia on clinical outcomes in venous thromboembolism: Results from GARFIELD-VTE

Shinya Goto [a,*], Alexander G.G. Turpie [b], Alfredo E. Farjat [c], Jeffrey I. Weitz [d], Sylvia Haas [e], Walter Ageno [f], Samuel Z. Goldhaber [g], Pantep Angchaisuksiri [h], Gloria Kayani [i], Peter MacCallum [j], Sebastian Schellong [k], Henri Bounameaux [l], Lorenzo G. Mantovani [m,n], Paolo Prandoni [o], Ajay K. Kakkar [p], on behalf of the GARFIELD-VTE investigators

[a] *Shinya Goto, Department of Medicine (Cardiology), Tokai University School of Medicine, Japan*
[b] *McMaster University, Hamilton, Canada*
[c] *Thrombosis Research Institute, London, United Kingdom*
[d] *McMaster University and the Thrombosis and Atherosclerosis Research Institute, Hamilton, Ontario, Canada*
[e] *Formerly Technical University of Munich, Munich, Germany*
[f] *Department of Medicine and Surgery, University of Insubria, Varese, Italy*
[g] *Harvard Medical School, Boston, USA*
[h] *Department of Medicine, Ramathibodi Hospital, Mahidol University, Thailand*
[i] *Thrombosis Research Institute, London, United Kingdom*
[j] *Thrombosis Research Institute, London, United Kingdom*
[k] *Medical Department 2, Municipal Hospital Dresden, Germany*
[l] *Faculty of Medicine, University of Geneva, Switzerland*
[m] *IRCCS Multimedica, Milan, Italy*
[n] *University of Milano, Bicocca, Milan, Italy*
[o] *Arianna Foundation on Anticoagulation, Bologna, Italy*
[p] *University College London, London, United Kingdom*

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ABSTRACT

Introduction: Clinical characteristics and outcomes of venous thromboembolism (VTE) patients with concomitant anemia are unclear. This study compares baseline characteristics, treatment patterns, and 24-month outcomes in patients with and without anemia within GARFIELD-VTE.

Materials and methods: GARFIELD-VTE (ClinicalTrials.gov: NCT02155491) is a global, prospective, non-interventional registry of real-world treatment practices. Of the 10,679 patients enrolled in GARFIELD-VTE, 7698 were eligible for analysis. Primary outcomes were all-cause mortality, recurrent VTE, and major bleeding in VTE patients with or without concomitant anemia over 24-months after diagnosis. Event rates and 95% confidence intervals were estimated using Poisson regression. Adjusted hazard ratios were calculated using Cox proportional hazard models.

Results: Distribution of VTE events in 2771 patients with anemia and 4927 without anemia was similar (deep-vein thrombosis alone: 61·1% vs. 55·9%, pulmonary embolism ± deep vein thrombosis: 38·9% vs. 44·0%, respectively). Patients with anemia were older (62.6 year vs. 58.9 years) than those without. At baseline, VTE risk factors that were more common in patients with anemia included hospitalization (22·0% vs. 6·8%), surgery (19·2% vs. 8·2%), cancer (20·1% vs. 5·6%) and acute medical illness (8·3% vs. 4·2%). Patients with anemia were more likely to receive parenteral anticoagulation therapy alone than those without anemia (26·6% vs. 11·7%) and less likely to receive a direct oral anticoagulant (38·5% vs. 53·5%). During 24-months of follow-up, patients with anemia had a higher risk (adjusted hazard ratio [95% confidence interval]) of all-cause mortality (1·84 [1·56–2·18]), major bleeding (2·83 [2·14–3·75]). Among anemia patients, the risk of all-cause mortality and major bleeding remained higher in patients with severe anemia than in those with mild/moderate anemia, all-cause mortality: HR 1·43 [95% CI: 1·21–1·77]; major bleeding: HR 2·08 [95% CI: 1·52–2·86]).

* Corresponding author at: Department of Medicine (Cardiology), Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan.
E-mail address: shinichi@is.icc.u-tokai.ac.jp (S. Goto).

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Conclusions: VTE patients with concomitant anemia have a higher risk of adverse clinical outcomes compared with those without anemia. Further optimization of anticoagulation therapy for VTE patients with anemia is warranted.

1. Introduction

Venous thromboembolism (VTE), which encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common cause of cardiovascular death worldwide [1,2]. VTE patients are at high risk of death and recurrent VTE [3,4]. Although anticoagulation is the mainstay of treatment for VTE and is critical for preventing death and recurrent VTE, anticoagulants increase the risk of bleeding events. The introduction of the direct oral anticoagulants (DOACs) has simplified extended duration anticoagulation therapy. In phase III trials, DOACs were at least as effective as vitamin K antagonists (VKA) for the treatment of VTE and were associated with a reduced risk of major bleeding [5–8]. However, because patients at high risk of bleeding or with severe anemia were excluded from these trials, the generalizability of these results remains uncertain.

We analyzed the Global Anticoagulant Registry in the FIELD (GARFIELD-VTE) database to study current anticoagulation treatment patterns in patients with anemia and to determine the impact of anemia on long-term outcomes in VTE. Thus, the baseline clinical characteristics, anticoagulation treatment patterns, and 24-month clinical outcomes (all-cause mortality, recurrent VTE, and major bleeding) in VTE patients with and without anemia were compared.

2. Methods

2.1. Study design and participants

The GARFIELD-VTE registry (ClinicalTrials.gov identifier: NCT02155491) design has been previously published [9]. The registry enrolled 10,685 VTE patients ≥18 years of age from 415 sites across 28 countries worldwide. Patients were considered eligible if an objective diagnosis of VTE was made within ±30 days of entry into the registry. Major exclusion criteria were: 1) patients for whom long-term follow-up was not planned, 2) patients without measured hemoglobin values, or 3) patients with hemoglobin values measured outside the 30-day window of entry into the registry.

2.2. Selection of study sites

The national coordinating investigator identified care settings to accurately represent the management of VTE patients in their country. The contract research organization provided a list of sites that reflected these care settings before contacting a random sample of sites for each care setting. Sites that agreed to participate were recruited after a qualification telephone call. Investigators were required to complete an educational program providing guidance on patient screening, enrolment, and follow-up in the registry.

2.3. Data collection

Patient data were collected using an electronic case report form (eCRF) designed by eClinicalHealth Services, Stirling, UK and submitted electronically via a secure website to the registry-coordinating center at the Thrombosis Research Institute (TRI), London, UK. TRI was responsible for ensuring complete and accurate data collection from the medical records of enrolled patients. The GARFIELD-VTE protocol mandates that 10% of all eCRFs are verified with source documentation, that electronic audit trails are available for all data modification, and that critical variables are subjected to additional audit. The data were extracted from the study database on 14th October 2020.

2.4. Ethics statement

The registry is 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), and adheres to all applicable national laws and regulations. Independent ethics committee for each participating country and the hospital-based institutional review board approved the design of the registry. All patients provided written informed consent to participate.

2.5. Definition of anemia

Anemia was diagnosed and classified based on hemoglobin (Hb) values attained on or prior to commencing anticoagulation treatment. Anemia was defined as Hb values <12 g/dL for women and <13 g/dL for men [10]. Severe anemia was defined as Hb values <10 g/dL for both men and women [11].

2.6. Clinical outcomes

The primary clinical outcomes were all-cause mortality, recurrent VTE, and major bleeding in patients with and without anemia over 24-months from VTE diagnosis. Major bleeding was defined as clinically overt bleeding associated with a critical site, a fall in hemoglobin of ≥2 g/dL, transfusion of 2 or more units of red blood cells, hemorrhagic stroke, or fatal outcome. Secondary clinical outcomes included non-major bleeding (any bleeding that did not meet the major bleeding criteria), myocardial infarction (MI)/acute coronary syndrome (ACS), and non-hemorrhagic stroke/transient ischemic attack (TIA), and cancer. Additionally, information was captured regarding the cause of death and sites of major bleeding. Cancer events that were diagnosed >30 days after the VTE diagnosis date were considered as cancer endpoints. Patients with cancer prior to the VTE diagnosis date or ≤ 30 days after the VTE diagnosis date were considered to have a history of cancer or active cancer, respectively. Only the first occurrence of each outcome event type was considered.

2.7. Statistical analysis

Continuous variables are summarized with their median and interquartile range (IQR), and categorical variables are presented as frequency and percentage. Creatinine clearance was estimated using the Cockcroft-Gault formula. Event rates and the associated 95% confidence interval (CI) were estimated using Poisson regression and are expressed per 100-person years.

Time-to-event analyses of outcomes were performed with Cox proportional hazard models following the intention-to-treat concept. Hazard ratios (HR) for each outcome were adjusted for the cofounders outlined in Supplemental Table S1. Missing values were imputed using the multivariate imputation by chain equations [12]. Model assumptions were tested to evaluate the adequacy of the observed data. Cumulative incidence plots were estimated to account for the competing risk of mortality on recurrent VTE and major bleeding. All statistical analyses were performed using R statistical software [13] and SAS® software version 9·4 (SAS Institute Inc., Cary, NC, USA). In all cases, two sided tests were used and the threshold for assessing statistical significance was set at the 5% level.

2.8. Role of the funding source

The funding sponsor had no involvement in the study design, collection, analysis or interpretation of data, writing the report, or the decision to submit the paper for publication.

3. Results

3.1. Baseline characteristics and care settings

Objectively confirmed VTE was diagnosed in 10,679 patients enrolled in the GARFIELD-VTE registry. Of these, 7698 (72·1%) were eligible for analysis in this study; 2771 (36·0%) with anemia and 4927 (64.0%) without anemia (Fig. 1). Patients with anemia were more likely to be older than those without anemia (median age 62·6 years vs. 58·9 years, respectively).

Baseline characteristics are displayed in Table 1. The sites of VTE events in patients with and without anemia were similar for DVT alone (61·1% and 56·0, respectively) and PE ± DVT (38·9% and 44·0%, respectively). DVT in both groups occurred mostly in the lower limbs (91·3% and 93·5%). Of patients with low hemoglobin, 1958 had mild/moderate anemia and 813 had severe anemia (Supplemental Table S2).

Persistent provoking risk factors (active cancer) and predisposing risk factors for VTE were more prominent in patients with anemia. Of those with anemia, 20·1% had active cancer and 22·4% had a history of cancer compared with 5·6% and 9·2%, respectively, in those without anemia. Patients with anemia more often had a history of heart failure (4·2 vs. 2·5%), immobilization (8·2% vs 4·0%), and renal insufficiency (6·6% vs. 2·4%) than those without anemia. Prior VTE was less prevalent in patients with anemia than in those without (10·0% vs. 17·9%). With the exceptions of hospitalization and surgery, which were more prevalent in patients with anemia than in those without (hospitalization: 22·0% vs. 6·8%; surgery: 19·2% vs. 8·2%, respectively), all other transient provoking risk factors were comparable between groups (Table 2).

3.2. VTE treatment patterns

After diagnosis of VTE, 98·2% of patients with anemia and 98·8% of those without anemia were started on anticoagulation therapy (Fig. 2). At baseline, a greater proportion of patients with anemia received parenteral therapy alone, compared to those without anemia (26·6% vs. 11·7%).

The use of VKA (alone or with parenteral therapy) was comparable in patients with and without anemia (alone: 5·7% vs. 5·0%; with parenteral therapy: 25·6% vs. 28·1%, respectively). The use of DOACs (alone or with parenteral therapy) was numerically lower in patients with anemia (alone: 24·5% vs. 32·8%; with parenteral therapy: 14·0% vs. 20·7%, respectively). The distribution of DOAC use according to type of dosage is reported in Supplemental Table S3.

The percentages of patients with anemia who remained on anticoagulant treatment was numerically lower than those without anemia at 3 months (82·4% vs. 91·6%), 6 months (68·0% vs. 77·9%), 12 months (49·0% vs. 58·9%), and 24-months (40·0% vs. 51·2%).

3.3. Clinical outcomes

At the 24-month follow-up, the unadjusted rates (95% CI) of all-cause mortality and major bleeds were numerically higher in patients with anemia than in those without (all-cause mortality: 11·02 vs. 2·76 per 100 person-years; major bleed: 3·84 vs. 0·95 per 100 person years) (Table 3). Patients with both mild/moderate and severe anemia who received NOAC treatment were numerically least likely to experience a major bleed (1·96% (95% CI: 1.34–2.86) and 5·16% (95% CI 3.33–8.00), respectively) compared with those prescribed with VKAs (2·34% (95% CI: 1.56–3.53) and 8.21% (95% CI: 5.71–11.82), respectively) or parenteral therapy (5.28% (95% CI: 3.79–7.36) and 7.01% (95% CI: 4.57–10.75), respectively) (Supplemental Table S4). The rate of recurrent VTE was similar between groups (4·64 vs. 4·21 per 100 person years) (Table 3).

After adjustment for cancer status, age, ethnicity, and BMI, the incidence rates for all-cause mortality (HR 1·84 [95% CI: 1·56–2·18]) and major bleeding (HR 2·83 [95% CI: 2·14–3·75]) remained higher in patients with anemia (Fig. 3).

The rate of recurrent VTE was comparable between groups. The cumulative incidence curves for the unadjusted rates of each of these primary outcomes are illustrated in Fig. 4. Patients with anemia also experienced any bleeds, MI/ACS, and stroke/TIA more frequently than patients without anemia (HR 1·41 [95% CI: 1·23–1·62]; HR 2·01 [95% CI: 1·21–3·34], and HR 1·56 [95% CI: 1·01–2·41]), respectively.

The most common sites of major bleeding in patients with and without anemia were the upper gastrointestinal (GI) tract (17·1% vs. 10·7%) and the lower GI tract (17·7% vs. 13·1%) (Supplemental

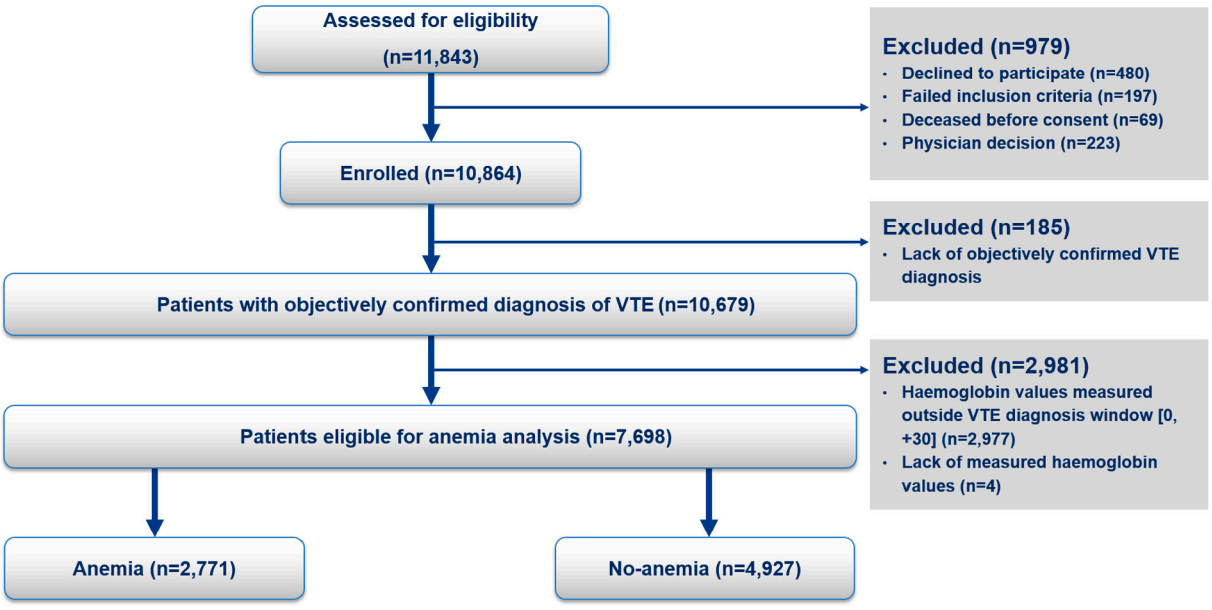


Fig. 1. Study population flowchart.

Table 1
Baseline characteristics. BMI, body mass index; DVT, deep vein thrombosis, PE, pulmonary embolism; VTE, venous thromboembolism.

Variable	Anemia (*n* = 2771)	No-anemia (*n* = 4927)
Male, n (%)	1178 (42·5)	2764 (56·1)
Age, median (IQR)	62·6 (47·0 to 74·0)	58·9 (46·0 to 69·9)
Age groups, n (%)		
<50	810 (29·2)	1580 (32·1)
50–65	712 (25·7)	1580 (32·1)
65–75	621 (22·4)	1014 (20·6)
75–85	485 (17·5)	618 (12·5)
>85	143 (5·2)	135 (2·7)
BMI, kg/m^2, median (IQR)	26·4 (22·9 to 30·8)	28·0 (24·9 to 32·1)
BMI categories, n (%)		
Underweight (<18.5 kg/m^2)	114 (4.4)	38 (0.9)
Normal (18.5–24.9 kg/m^2)	940 (36.5)	1144 (25.7)
Overweight (25.0–29.9 kg/m^2)	788 (30.6)	1667 (37.5)
Obese (≥ 30 kg/m^2)	733 (28.5)	1599 (35.9)
Missing	196	479
Smoking, n (%)		
Ex-smoker	654 (24·1)	1051 (22·2)
Current smoker	310 (11·4)	892 (18·8)
Missing	61	191
VTE type, n (%)		
DVT	1693 (61·1)	2755 (55.9)
PE ± DVT	1078 (38·9)	2172 (44.0)
Site of DVT, n (%)		
Upper limb	130 (6·2)	173 (4·7)
Lower limb	1920 (91·3)	3425 (93·6)
Caval vein	53 (2·5)	63 (1·7)
Missing	668	1266
Type of lower limb DVT		
Distal	609 (32.0)	1189 (35·1)
Proximal	725 (38·1)	1218 (36·0)
Both	567 (29.8)	978 (28·9)
Missing	870	1540
Site of PE (pulmonary arterial branch, n (%)		
Main	299 (27.9)	694 (32·2)
Lobar	311 (29.0)	655 (30·4)
Segmental	359 (33·5)	618 (28·7)
Sub-segmental	103 (9·6)	189 (8·8)
Missing	1699	2771
Care setting, n (%)		
Hospital	2205 (79·6)	3685 (74·8)
Outpatient setting	566 (20·4)	1242 (25·2)
Specialty, n (%)		
Vascular medicine	1137 (41·0)	2163 (43·9)
General practitioner	132 (4.8)	138 (2·8)
Internal medicine (haematology and intensive care)	1304 (47·1)	2245 (45·6)
Emergency medicine	76 (2·7)	146 (3·0)
Cardiology	122 (4·4)	231 (4·7)
Missing	0	4
Region, n (%)		
Africa and Middle East	308 (11·1)	305 (6·2)
Asia	752 (27·1)	541 (11·0)
Europe	1214 (43·8)	3150 (63·9)
Latin America	87 (3·1)	132 (2·7)
North America/Australia	410 (14·8)	799 (16·2)
Creatinine clearance groups [ml/min][a]		
<15	47 (1·8)	51 (1·1)
15–30	129 (5·0)	73 (1·6)
30–50	313 (12·1)	284 (6·3)
>50	2091 (81·0)	4121 (91·0)
Missing	191	398
Hemoglobin categories [g/dL], n (%)		
Low (males: <13·0; females: <12·0)	2771 (100·0)	0 (0)
Platelets, median (IQR), [10^9/L], n (%)	247·0 (184·0 to 327·0)	224·0 (183·0 to 278·0)
Platelets categories [10^9/L], n (%)		
Thrombocytopenia (<150)	352 (12·9)	459 (9·4)
Normal (150–450)	2168 (79·3)	4325 (88·8)
Thrombocytosis (>450)	214 (7·8)	88 (1·8)
Missing	37	55

[a] Creatinine clearance was estimated using the Cockcroft-Gault formula.

Table 2
Risk factors associated with VTE. VTE, venous thromboembolism.

	Anemia (n = 2771)	No-anemia (*n* = 4927)
Persistent provoking risk factors, n (%)		
Active cancer	557 (20·1)	276 (5·6)
Transient provoking risk factors, n (%)		
Acute medical illness	229 (8·3)	208 (4·2)
Hospitalization	610 (22·0)	336 (6·8)
Long-haul travelling	61 (2·2)	350 (7·1)
Surgery	532 (19·2)	402 (8·2)
Trauma to the lower limb	189 (6·8)	385 (7·8)
Hormone replacement therapy	48 (1·7)	81 (1·6)
Oral contraception	101 (3·6)	299 (6·1)
Predisposing risk factors, n (%)		
Chronic heart failure	117 (4·2)	124 (2·5)
Chronic immobilization	228 (8·2)	195 (4·0)
Family history of VTE	87 (3·1)	381 (7·7)
History of cancer	620 (22·4)	454 (9·2)
Known thrombophilia	61 (2·2)	165 (3·3)
Previous VTE	277 (10·0)	880 (17·9)
Renal insufficiency	183 (6.6)	117 (2.4)

Table S5). The most common causes of death in patients with and without anemia were cancer (55·3% vs. 47·4%) followed by cardiovascular events (7·2% vs. 8·9%) (Supplemental Table S6).

Of the 2771 patients with anemia, 1958 (70·7%) were characterized as having mild/moderate anemia and 813 (29·3%) as having severe anemia. The unadjusted rates of all-cause mortality and major bleeds were numerically lower in patients with mild/moderate anemia than in those with severe anemia (all-cause mortality: 8·85 vs 17·10, per 100 person-years; major bleed: 2·86 vs. 6·66, per 100 person-years, respectively) (Supplemental Table S7). After adjustment, the risk of all-cause mortality and major bleeding remained higher in patients with severe anemia than in those with mild/moderate anemia (all-cause mortality: HR 1·42 [95% CI: 1·17–1·72]; major bleeding: HR 1·84 [95% CI: 1·33–2·55]) (Supplemental Fig. S1). The frequency of any bleeds, VTE recurrence, cancer, MI/ACS, and stroke/TIA was comparable in both patient groups.

4. Discussion

We found that VTE in patients with concomitant anemia was more frequently associated with active cancer or a history of cancer, heart failure, chronic immobilization, renal insufficiency, and a history of hospitalization than VTE patients without anemia. Patients with anemia were also more likely to be treated with parenteral anticoagulants and VKAs and less likely to receive DOACs. Rates of mortality and severe bleeding were higher in patients with anemia than in those without, despite a similar risk of recurrent VTE.

Current guidelines recommend anticoagulation therapy for at least 3-months for most patients with VTE [14,15]. In GARFIELD-VTE, 17·6% of patients with anemia and 8·5% of those without anemia were not on anticoagulant therapy at 3-months, increasing to 59·4% and 48·8%, respectively, at 24-months. Patients with anemia experienced similar rates of VTE recurrence even with numerically lower use of oral anticoagulants after 3 months. Lower risk of VTE in anemia is not contradicted with previous publications suggesting a higher VTE event risk in patients with higher hematocrit value [16,17] Despite similar stopping rates, the choice of anticoagulant therapy differed between the two groups. The early separation of the Kaplan Meier curves for major bleeding suggests that underlying lesions prone to bleeding, such as occult cancer, are more frequently present in VTE patients with anemia. The upper/lower GI tract and uterus were the most frequent sites of bleeding both in patients with and without anemia, with higher rates found among those with anemia. More than half of deaths within the anemia group were attributed to cancer.

The prevalence of cancer in patients with anemia was higher than in those without. Although this may have accounted for the higher

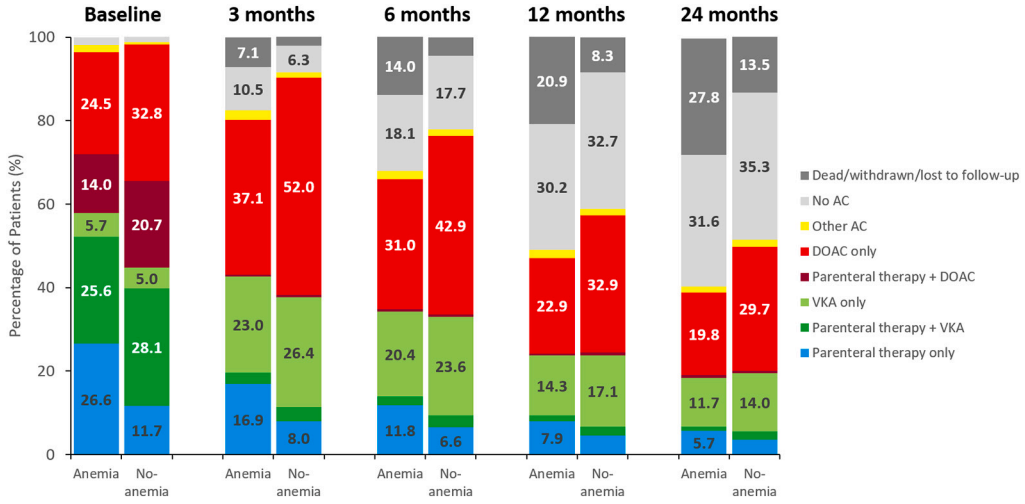


Fig. 2. Anticoagulation treatment patterns over 24 months' follow-up in VTE patients with or without concomitant anemia. Baseline refers to the first 30 days after VTE diagnosis. Abbreviations: AC; anticoagulant. DOAC; Direct oral anticoagulant, VKA; Vitamin K antagonist.

Table 3
Unadjusted 24-month clinical outcomes after VTE diagnosis. Event rates are shown per 100 person-years (95% confidence interval). CI; confidence interval, VTE; venous thromboembolism, MI; myocardial infarction, ACS; acute coronary syndrome, TIA; transient ischemic attack.

Outcome		Anemia (n = 2771)		No-anemia (n = 4927)
Event	n	Event rate (95% CI)	n	Event rate (95% CI)
All-cause mortality	488	11·02 (10·09 to 12·04)	247	2·78 (2·44 to 3·13)
Recurrent VTE	195	4·64 (4·03 to 5·34)	360	4·21 (3·79 to 4·66)
Major bleed	164	3·84 (3·29 to 4·47)	84	0·95 (0·77 to 1·17)
Any bleed	425	10·78 (9·80 to 11·85)	537	6·52 (5·99 to 7·09)
Cancer	114	2.63 (2·19 to 3·16)	159	1·80 (1·54 to 2·11)
MI/ACS	34	0·77 (0·55 to 1·08)	33	0·37 (0·26 to 0·52)
Stroke/TIA	45	1·02 (0·76 to 1·37)	47	0·53 (0·40 to 0·70)

mortality rate in VTE patients with anemia, the difference between the two groups persisted after adjustment for cancer. This suggests that alternative explanations are likely to play a key role in determining a poorer prognosis in VTE patients with anemia. One possibility is more frequent presence of occult cancer.

Previous reports from the RIETE registry (Registro Informatizado Enfermedad Tromboembólica) have also demonstrated a higher risk for major bleeding in patients with anemia compared to those without [18]. In the GARFIELD registry, a gradient was observed for the association of anemia severity, rates of major bleeding, and all-cause mortality. Adverse clinical outcomes occurred more frequently in patients with severe anemia than in those with mild/moderate anemia. Adjusting for co-variables, including cancer status, our results identify anemia as an independent risk factor for bleeding events in VTE. Similar to GARFIELD-VTE, COMMAND also showed an increase in major bleeding and mortality rates according to anemia severity [19]. Additionally, the APEX trial has shown that anemia was independently associated with a

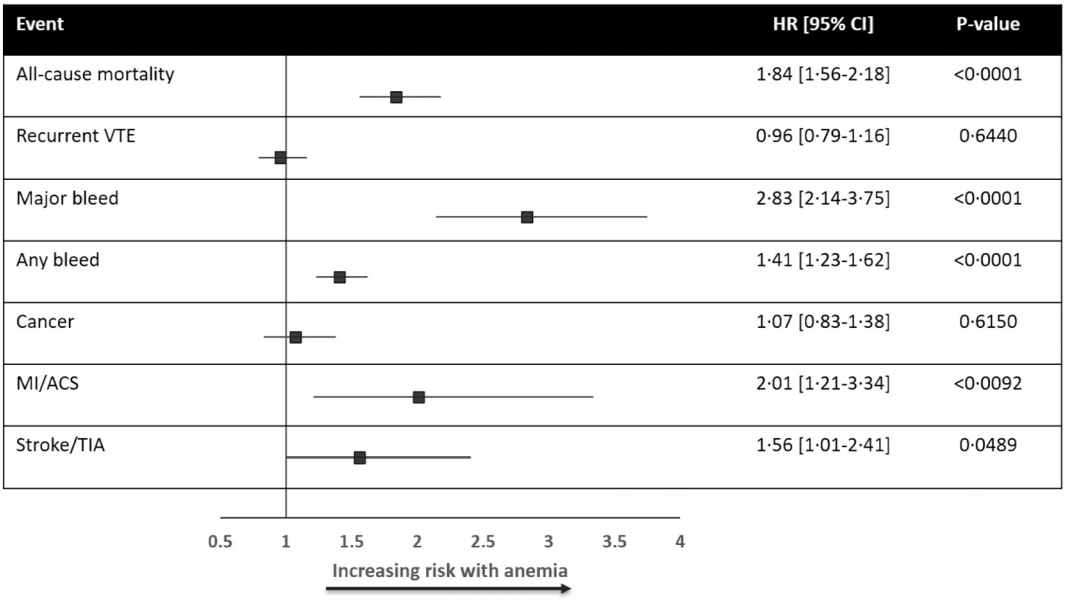


Fig. 3. Adjusted hazard ratios for mortality with 95% CIs for 24-month outcomes after VTE diagnosis between patients with anemia and or with no-anemia (reference group). Abbreviations: VTE; venous thromboembolism, TIA; transient ischemic attack, MI; myocardial infarction, ACS; acute coronary syndrome, HR; hazard ratio, CI; confidence interval.

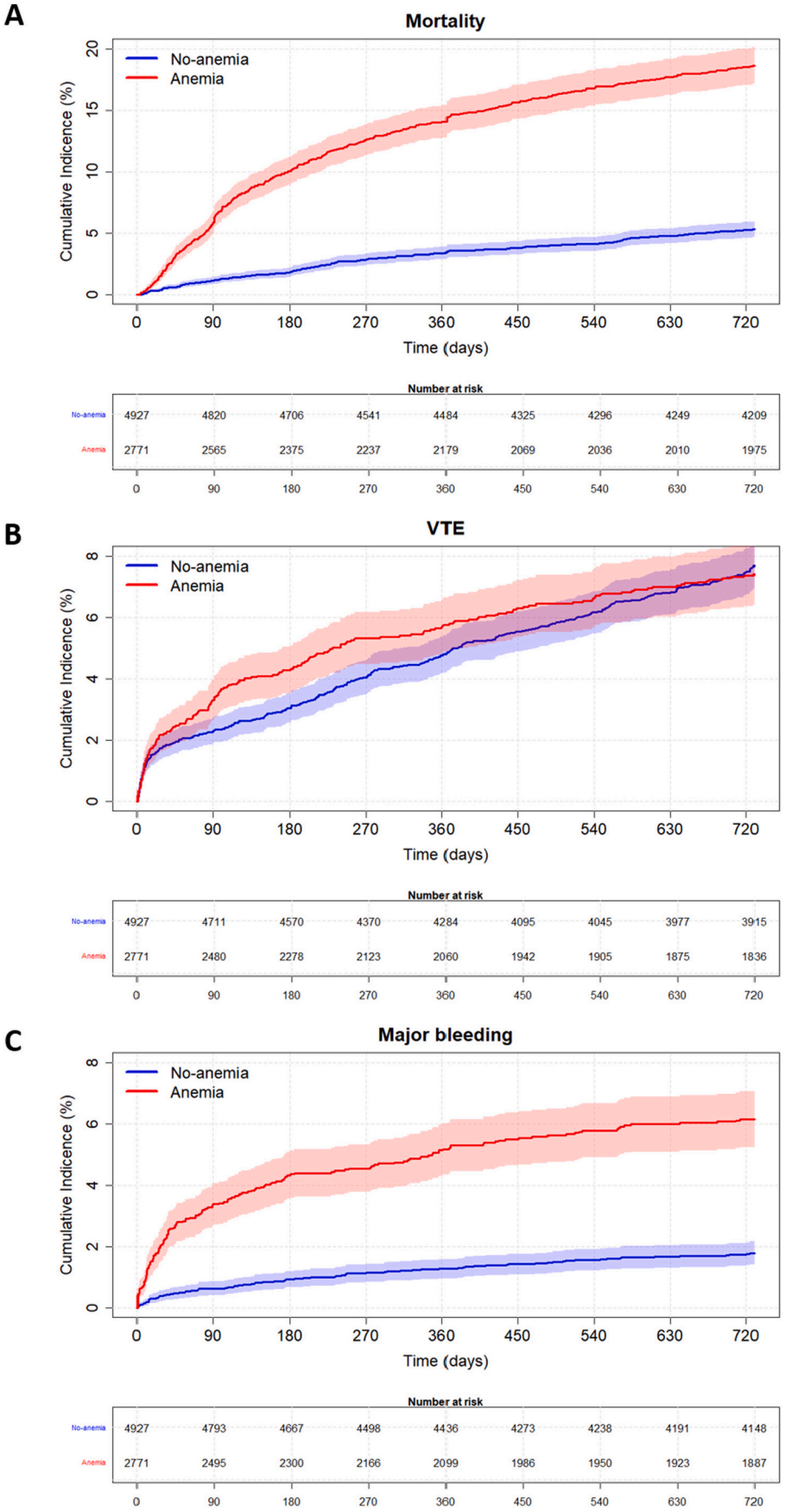


Fig. 4. Cumulative incidence of (a) all-cause mortality, (b) recurrent VTE and, (c) major bleeding over 24 months follow up in VTE patients with and without anemia. Unadjusted data of the cumulative incidence of events with 95% CI. VTE; venous thromboembolism. CI; confidence interval.

greater risk of VTE among acutely ill medical patients, despite the provision of thromboprophylaxis [20].

5. Strengths and limitations

This analysis has a number of important strengths and limitations. This study uses a real-world population of VTE patients, allowing an insight into the current outcomes and treatment protocols in a clinical setting. Additionally, in comparison to other registries, this study has the advantage of a large cohort size observed over the long follow-up period of 24-months. Limitations include the non-randomized collection of data associated with the registry and use of the intention-to-treat concept. The intention-to-treat approach does not account for treatment duration/discontinuation or for fluctuating Hb values after initial assessment at baseline. Another important limitation is that Hb values were available for only 7698 of the 10,679 patients in GARFIELD-VTE.

6. Conclusion

GARFIELD-VTE provides a comprehensive overview of current VTE management and clinical outcomes for VTE patients with anemia and includes analysis of DOAC usage. Baseline anemia is a prominent predictor of the risk of major bleeding and all-cause mortality but does not impact the risk of recurrent VTE. GARFIELD-VTE thus indicates the need for suitable management strategies to reduce the risk of major bleeding and mortality for VTE patients with concomitant anemia.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Appendix A. Supplementary data

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