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Full Length Article

36-month clinical outcomes of patients with venous thromboembolism: GARFIELD-VTE

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ABSTRACT

Background: Venous thromboembolism (VTE), encompassing both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a leading cause of morbidity and mortality worldwide.
Methods: GARFIELD-VTE is a prospective, non-interventional observational study of real-world treatment practices. We aimed to capture the 36-month clinical outcomes of 10,679 patients with objectively confirmed VTE enrolled between May 2014 and January 2017 from 415 sites in 28 countries.
Findings: A total of 6582 (61.6 %) patients had DVT alone, 4097 (38.4 %) had PE ± DVT. At baseline, 98.1 % of patients received anticoagulation (AC) with or without other modalities of therapy. The proportion of patients on AC therapy decreased over time: 87.6 % at 3 months, 73.0 % at 6 months, 54.2 % at 12 months and 42.0 % at 36 months. At 12-months follow-up, the incidences (95 % confidence interval [CI]) of all-cause mortality, recurrent VTE and major bleeding were 6.5 (7.0–8.1), 5.4 (4.9–5.9) and 2.7 (2.4–3.0) per 100 person-years, respectively. At 36-months, these decreased to 4.4 (4.2–4.7), 3.5 (3.2–2.7) and 1.4 (1.3–1.6) per 100 person-years, respectively. Over 36-months, the rate of all-cause mortality and major bleeds were highest in patients treated with parenteral therapy (PAR) versus oral anti-coagulants (OAC) and no OAC, and the rate of recurrent VTE was highest in patients on no OAC versus those on PAR and OAC. The most frequent cause of death after 36-month follow-up was cancer (n = 565, 48.6 %), followed by cardiac (n = 94, 8.1 %), and VTE (n = 38, 3.2 %). Most

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recurrent VTE events were DVT alone (n = 564, 63.3 %), with the remainder PE, (n = 236, 27.3 %), or PE in combination with DVT (n = 63, 7.3 %).
Interpretation: GARFIELD-VTE provides a global perspective of anticoagulation patterns and highlights the accumulation of events within the first 12 months after diagnosis. These findings may help identify treatment gaps for subsequent interventions to improve patient outcomes in this patient population.

1. Introduction

Venous thromboembolism (VTE), which includes deep-vein thrombosis (DVT) and pulmonary embolism (PE), is a leading cause of morbidity and mortality worldwide [1]. The annual incidence of VTE is estimated at 0.75–2.69 cases per 1000 adults per year [2], and VTE is responsible for >500,000 deaths each year in the European Union [3]. The goal of VTE treatment is to reduce the risk of the acute and long-term complications, including mortality and recurrent VTE. AC therapy is the mainstay of VTE treatment; a minority of patients may receive initial thrombolytic or other reperfusion therapies. Anticoagulation is given for at least 3 months, and treatment is extended if the risk of recurrence of VTE exceeds the risk of bleeding with continued therapy [4]. Contemporary VTE treatments are based largely on the results of randomized controlled trials [5–8]. Whilst essential for evaluating the safety and efficacy of each treatment, the highly selected patients enrolled in such trials do not represent those in everyday clinical practice. Uncertainty persists regarding the burden and patterns of treatment of VTE in the real world, and the long-term clinical outcomes of these patients.

The Global Anticoagulant Registry in the Field-Venous Thromboembolism (GARFIELD-VTE, ClinicalTrials.gov identifier: NCT02155491) was a global, prospective, multi-centre, observational study of VTE patients treated according to local standard practices [9]. The primary aim of the registry was to capture the initial, long-term and extended management strategies and clinical outcomes in patients with acute VTE treated in a real-world setting. Baseline characteristics of the cohort have been previously reported [10]. This study describes the clinical outcomes (including all-cause mortality, recurrent VTE, and major bleeding) after 36-months of follow-up.

2. Methods

2.1. Study design and participants

GARFIELD-VTE is a non-interventional, prospective, multicentre, observational registry designed to capture real-world outcomes of patients with acute VTE. The study design for GARFIELD-VTE has been described previously [9] and the registry was funded by an unrestricted research grant from Bayer AG. Men and women ≥18 years of age with an objectively confirmed diagnosis of VTE within 30 days of entry into the registry were eligible for inclusion. Patients with recurrent VTE must have completed treatment for the previous VTE episode. Those with superficial vein thrombosis or participating in an interventional study that dictated treatments, or for whom long-term follow up was not possible were excluded. Patients were managed according to local practices; no specific treatments, tests, or procedures were mandated by the protocol. Decisions to initiate, continue or change treatment were solely at the discretion of the treating physicians and their patients.

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 from 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 centre 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 mandated 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. Clinical outcomes

The primary clinical outcomes were all-cause mortality, recurrent VTE and major bleeding. Major bleeding was defined according to the International Society of Thrombosis and Haemostasis criteria [11]. Non-major bleeding was defined as overt bleeding not meeting the criteria for major bleeding. Recurrent VTE consisted of both symptomatic and asymptomatic VTE and was defined as a confirmed diagnosis of a VTE event after completion of treatment for a previous VTE episode. Secondary outcomes included non-major bleeding, newly diagnosed cancer, stroke/transient ischemic attack, myocardial infarction, and hospitalization. Information was collected regarding the cause of death, reasons for hospitalization, and nature of bleeding. Cancer events diagnosed >30 days after the VTE diagnosis date were considered as cancer endpoints. Patients were characterised as having active cancer if they were diagnosed and/or receiving treatment for their cancer ≤90 days before VTE diagnosis and up to 30 days after VTE diagnosis. Patients were defined as having a history of cancer if the cancer went into remission and the patient was not receiving any cancer treatment > 90 days before the diagnosis of VTE. All other patients were classified as not having cancer. Hospitalization was defined as admission to hospital for ≥2 days. For all other outcomes, events that occurred from the day of diagnosis onwards were considered as endpoints.

2.5. 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. Confidentiality and anonymity of patients recruited into this registry were maintained.

2.6. Statistical analysis

The analyses focused on patients with 36 months of follow-up, or those who died during this period. Other than all-cause mortality, a patient can have more than one recurrence or major bleed; however, only the first occurrence of each type was considered. Patient

demographics, clinical characteristics at baseline and outcomes were summarized into frequency tables (ordinal or nominal data) along with percentages of the total. Event rates are expressed in 100-person years with the associated 95 % confidence interval (CI). This study is descriptive in nature and no formal testing for significance was performed. Analyses were performed using SAS® statistical software version 9.1.3 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient enrolment

A total of 11,843 patients were assessed for eligibility, of whom 10,864 were enrolled between 12th May 2014 and 4th January 2017; 979 patients were excluded because they did not meet the inclusion or exclusion criteria (n = 197), died before consent could be obtained (n = 69), or because participation was declined by the patient (n = 480) or the treating physician (n = 233). An additional 184 patients were excluded because the diagnosis of VTE was not objectively confirmed using the criteria defined by Bates et al. [12] (Fig. 1). The remaining 10,679 patients were followed for 36 months and constituted the final data set for analyses.

3.2. Baseline characteristics

The baseline characteristics have been described in detail previously [13]. Briefly, a total of 6582 (61.6 %) patients had DVT alone, 4097 (38.4 %) had PE ± DVT. DVT involved the lower limb in 92.9 % of cases, with the remainder involving an upper limb (5.3 %) or the vena cava (1.8 %). Of those with lower limb DVT, 36.8 % had proximal DVT, 35.4 % had distal DVT, and 27.8 % had both proximal and distal DVT. More patients were treated in a hospital setting than in the outpatient setting (73.2 % and 26.8 %, respectively). Most patients were treated by specialists in vascular medicine (44.8 %) or internal medicine, including haematology and intensive care (43.4 %). Patients were predominantly enrolled from Europe (56.1 %), followed by Asia (17.0 %), North America/Australia (13.5 %) and Africa and the Middle East (9.8 %). The most predominant risk factors were a history of VTE (15.2 %), a history of cancer (13.3 %) recent surgery (12.5 %), hospitalization (12.1 %), or active cancer (10.2 %) (Table 1).

3.3. Treatment patterns

At baseline, 98.2 % of patients received anticoagulation (AC) with or without other modalities of therapy, with 17 % receiving parenteral AC only and 42.6 % receiving parenteral and oral AC. The proportion of patients receiving AC therapy decreased over time: 87.5 % at 3 months, 73.1 % at 6 months, 54.3 % at 12 months and 41.9 % at 36 months

Table 1
Baseline characteristics.

Variable, n (%)	Overall (N = 10,679)
VTE diagnosis	
DVT	6582 (61.6 %)
PE	2457 (23.0 %)
DVT and PE	1640 (15.4 %)
Site of DVT	
Lower limb	7629 (92.9 %)
Upper limb	436 (5.3 %)
Caval vein (inferior)	100 (1.2 %)
Caval vein (superior)	49 (0.6 %)
Type of lower limb DVT	
Proximal	2780 (36.8 %)
Distal	2669 (35.4 %)
Both	2101 (27.8 %)
Pulmonary arterial branch involved	
Main	1206 (29.7 %)
Lobar	1202 (29.6 %)
Segmental	1272 (31.3 %)
Sub-segmental	387 (9.5 %)
Care setting	
Hospital	7817 (73.2 %)
Outpatient setting	2862 (26.8 %)
Specialty	
Vascular medicine	4784 (44.8 %)
General practitioner	381 (3.6 %)
Internal medicine (haematology and intensive care)	4629 (43.4 %)
Emergency medicine	275 (2.6 %)
Cardiology	605 (5.7 %)
Missing	5
Region	
Africa and Middle East	1044 (9.8 %)
Asia	1820 (17.0 %)
Europe	5990 (56.1 %)
Latin America	382 (3.6 %)
North America/Australia	1443 (13.5 %)
Risk factors	
Prior episode of DVT and/or PE	1621 (15.2 %)
History of cancer	1417 (13.3 %)
Surgery	1330 (12.5 %)
Hospitalization	1296 (12.1 %)
Active cancer	1090 (10.2 %)
Trauma of the lower limb	829 (7.8 %)
Family history of VTE	648 (6.1 %)
Acute medical illness	606 (5.7 %)
Chronic immobilization	610 (5.7 %)
Oral contraception (females)	532 (5.0 %)
Long-haul travelling	527 (4.9 %)
Renal insufficiency	391 (3.7 %)
Recent bleed or anemia	370 (3.5 %)
Chronic heart failure	338 (3.2 %)
Known thrombophilia	315 (2.9 %)
Hormone replacement therapy (females)	169 (1.6 %)

DVT = deep vein thrombosis. MI = myocardial infarction. PE = pulmonary embolism. VTE = venous thromboembolism.

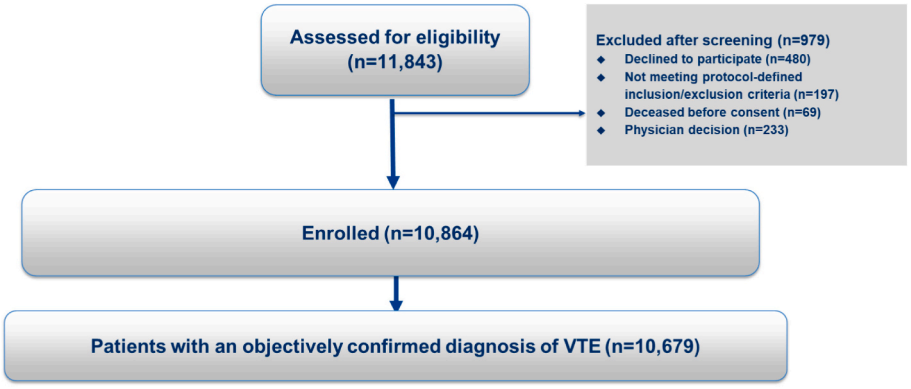


Fig. 1. Patient enrolment flowchart.
VTE = venous thromboembolism.

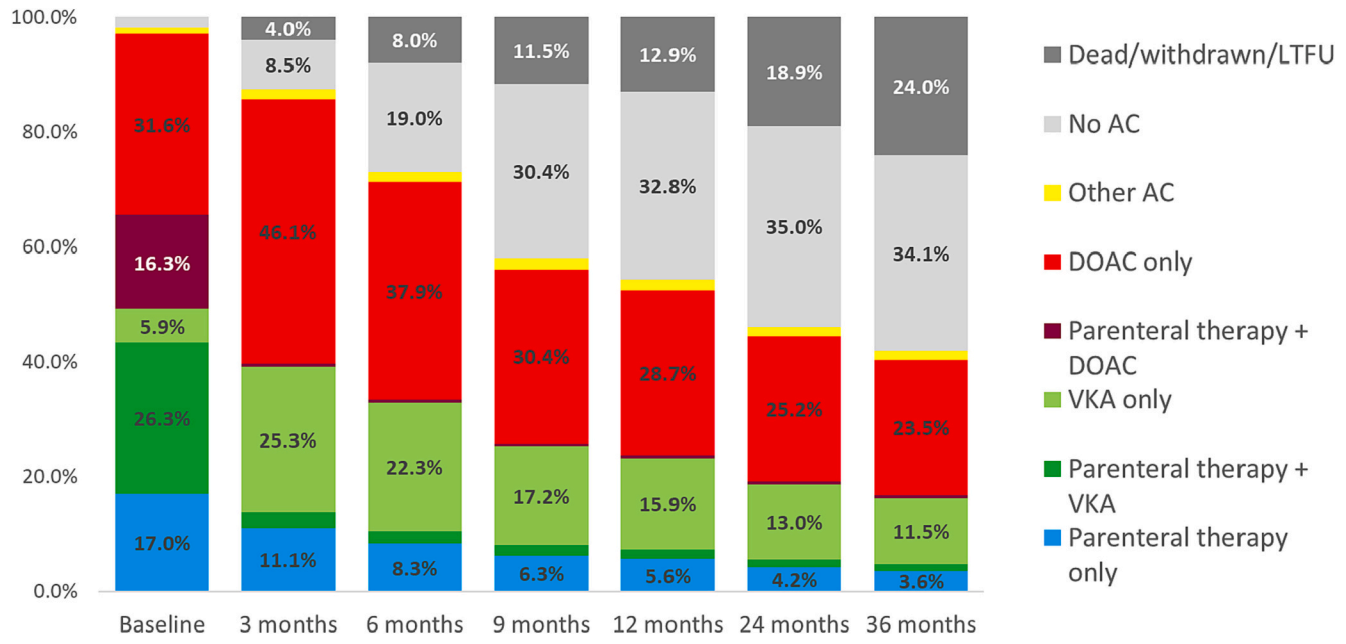


Fig. 2. Anticoagulation treatment patterns at baseline and follow-up visits.
AC = anticoagulant, VKA = vitamin K antagonist, DOAC = direct oral anticoagulant, LTFU = lost to follow-up.

(Fig. 2). After 12-months, over half of all patients remaining on AC therapy were receiving a direct oral anticoagulant (DOAC) (12 months: 52.9 %, 24 months: 54.8 %, 36 months: 56.1 %), with a smaller proportion receiving a vitamin K antagonist (VKA) (12 months: 32.4 %, 24 months: 31.3 %, 36 months: 30.2 %).

3.4. All-cause mortality

Over 36 months, a total of 1163 (10.9 %) patients died. The rate of all-cause mortality was higher in the first month of follow-up than in the subsequent 11-months (10.69 [8.72–13.1] per 100 person-years vs. 6.54 [6.05–7.07] per 100 person-years, respectively). Similarly, the rate was higher in the first year (months 1–12) of follow-up (7.5 [6.97–8.06] per 100 person-years) than in the second year (months 13–24) (3.1 [2.75–3.50] per 100 person-years) or third year (months 25–36) of follow-up (2.0 (1.72–2.34) per 100 person-years) (Table 2). Fig. 3 shows the cumulative incidence of all-cause mortality over 36 months of follow-up and the corresponding number at risk. At each milestone, cancer was the leading cause of death; 42 % at 1-month, 53 % at 12-months, and 48.6 % at 36-months (Table 3). Over the 36-month follow-up period the event rate per 100 person-years for all-cause mortality was highest in patients who were on PAR compared to those on OAC or no OAC (12.09, 2.91, and 7.43 respectively) (Table 5).

3.5. Recurrent VTE

Fig. 3 shows the cumulative incidence of recurrent VTE over 36 months of follow-up and the corresponding number at risk. Of the 866 events, 564 (65.1 %) were DVT, 236 (27.3 %) were PE and 63 (7.3 %) were both DVT and PE. Patients treated with no OAC had the highest rate per 100-person-years of recurrent VTE compared to those treated with OAC and PAR (6.26 vs 3.25 and 4.3, respectively) (Table 5).

3.6. Major bleeding

Fig. 3 shows the cumulative incidence of major bleeding over 36 months of follow-up and the corresponding number at risk. The most common sites of major bleeding were the upper and lower GI tract (15.4 % and 16.2 %, respectively). Haemorrhagic stroke accounted for 20 (5.5 %) major bleeds (Table 4). Patients treated with OAC had the lowest rate per 100 person-years of major bleeding compared to PAR and no OAC (1.17 vs 2.67 and 2.16, respectively) (Table 5).

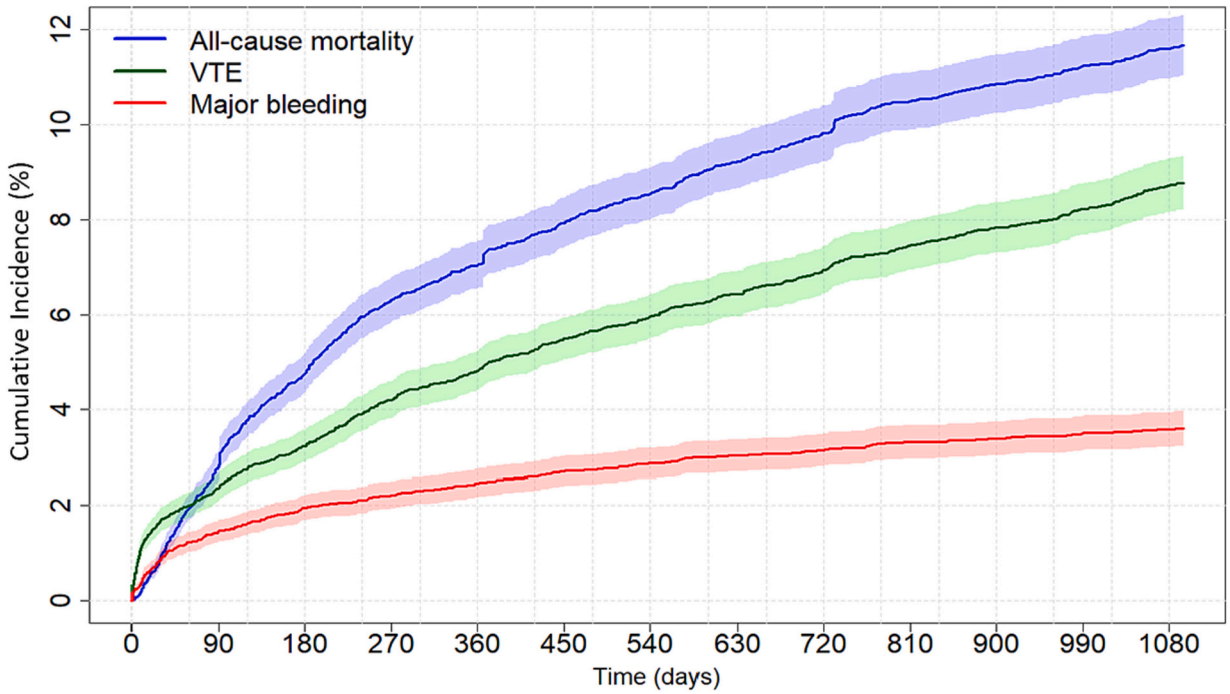
3.7. Other events

There were 1052 non-major bleeding events, equivalent to a rate of 4.32 (4.07–4.59) per 100 person-years. The most common sites of non-major bleeding were epistaxis (17 %), macroscopic haematuria (13.9 %)

Table 2
Clinical outcomes over 36-months follow-up. Rates are per 100-person year.

	Year 1 (0–12 months)		Year 2 (13–24 months)		Year 3 (25–36 months)		Overall (0–36 months)	
	Events	Rate (95 % CI)	Number of events	Rate (95 % CI)	Events	Rate (95 % CI)	Events	Rate (95 % CI)
All-cause mortality	732	7.5 (6.97 to 8.06)	270	3.1 (2.75 to 3.5)	159	2.0 (1.72 to 2.34)	1161	4.4 (4.15 to 4.66)
Recurrent VTE[a]	505	5.34 (4.89 to 5.82)	209	2.55 (2.23 to 2.92)	152	2.08 (1.77 to 2.43)	866	3.47 (3.24 to 3.7)
Major bleed	258	2.68 (2.37 to 3.02)	68	0.8 (0.63 to 1.01)	37	0.48 (0.35 to 0.66)	363	1.4 (1.26 to 1.55)
Non-Major bleed	821	8.9 (8.31 to 9.53)	143	1.8 (1.53 to 2.12)	88	1.23 (1.00 to 1.52)	1052	4.32 (4.07 to 4.59)
New cancer[b]	259	2.69 (2.38 to 3.03)	106	1.25 (1.03 to 1.51)	72	0.93 (0.74 to 1.18)	437	1.69 (1.54 to 1.86)
Stroke/TIA	69	0.71 (0.56 to 0.9)	50	0.58 (0.44 to 0.76)	39	0.50 (0.36 to 0.68)	158	0.6 (0.52 to 0.70)
MI	70	0.72 (0.57 to 0.91)	26	0.3 (0.2 to 0.44)	33	0.42 (0.3 to 0.59)	129	0.49 (0.41 to 0.58)

MI = myocardial infarction. TIA = transient ischemic attack. VTE = venous thromboembolism.
[a] Some recurrent VTEs were both PEs and DVT, therefore they are counted as both DVT events and PE events.
[b] Only cancer events that were diagnosed >30 days from VTE diagnosis date are considered cancer endpoints.



Number at risk

	0	90	180	270	360	450	540	630	720	810	900	990	1080
All-cause mortality	10679	10233	9801	9350	9209	8810	8712	8616	8515	8009	7926	7825	7822
Recurrent VTE	10679	9997	9502	8978	8785	8344	8216	8090	7955	7430	7320	7240	7151
Major bleeding	10679	10113	9663	9205	9047	8637	8530	8429	8322	7817	7729	7674	7623

Fig. 3. Cumulative incidence curves with 95 % confidence intervals of primary outcomes over 36 months' follow-up.
VTE = venous thromboembolism.

Table 3
Cause of death. The data are the occurrence and percent of patients with a cause of death during that time period.

Cause of death	1 month (N = 100)	12 months (N = 732)	36 months (N = 1163)
Cancer	42 (42)	388 (53)	565 (48.6)
Cardiac	10 (10)	45 (6.1)	94 (8.1)
Bleed	4 (4)	32 (4.4)	46 (4.0)
VTE	10 (10)	29 (3.9)	38 (3.2)
Other	23 (23)	134 (18.3)	222 (19.1)
Unknown	11 (11)	104 (14.2)	198 (17.0)

Fatal bleeds include haemorrhagic stroke. VTE includes pulmonary embolism and other VTE complications.
VTE = venous thromboembolism.

and lower GI tract bleeding (12 %) (Appendix Table A1).

A total of 437 patients developed cancer (diagnosed >30 days after VTE diagnosis), at a rate of 1.69 (1.54–1.86) per 100 person-years. The rates of stroke/transient ischemic attacks (TIA) and myocardial infarctions (MI) were low; 0.6 (0.52–0.70) per 100 person-years and 0.49 (0.41–0.58) per 100 person-years, respectively. Patients treated with OAC had the lowest rate per 100 person-years of stroke/TIA (0.54), MI (0.45), DVT (2,28), and PE events (1.15) compared to patients treated with PAR (0.74, 0.61, 3.09, and 1.46, respectively) and no OAC (2.34, 1.89, 4.67, and 1.67, respectively) (Table 5).

Table 4
Site of major bleeding. The data are the occurrence and percent of patients with a major bleed during that time period.

Site of major bleed	12 months (N = 258)	36 months (N = 363)
Intra-spinal	4 (1.6)	5 (1.4)
Intra-ocular/retinal	8 (3.1)	12 (3.3)
GI upper	41 (15.9)	56 (15.4)
GI lower	40 (15.5)	59 (16.2)
Macroscopic haematuria	13 (5)	19 (5.2)
Metro-menorrhagia	124 (15.1)	137 (13)
Intra-articular	3 (1.2)	8 (2.2)
Intra-muscular (no compartment syndrome)	7 (2.7)	7 (1.9)
Intra-muscular (with compartment syndrome)	6 (2.3)	6 (1.6)
Epistaxis	3 (1.2)	5 (1.4)
Gingival	3 (1.2)	3 (0.8)
Intra-peritoneal	5 (1.9)	7 (1.9)
Retro-peritoneal	7 (2.7)	12 (3.3)
Puncture site	2 (0.8)	4 (1.1)
Skin (ecchymosis other than instrument site)	3 (1.2)	4 (1.1)
Haemoptysis	9 (3.5)	9 (2.5)
Haemopericardium	4 (1.6)	4 (1.1)
Haemothorax	4 (1.6)	5 (1.4)
Haemorrhagic stroke	10 (3.9)	20 (5.5)
Other	38 (14.7)	63 (17.3)
Unknown	16 (6.2)	19 (5.2)

GI = gastrointestinal.

Table 5
Unadjusted events and event rates from 0 to 36 months according to treatment.

Endpoint	Overall (0–36 months) (n = 10,387)		PAR (n = 1788)		OAC (n = 8410)		No AC (n = 189)	
	Number of events	Rate per 100 person-years	Number of events	Rate per 100 person-years	Number of events	Rate per 100 person-years	Number of events	Rate per 100 person-years
All-cause mortality	1118	4.34	458	12.09	628	2.91	32	7.43
Cancer[a]	430	1.7	99	2.69	322	1.52	9	2.14
Bleeding	1324	5.67	222	6.39	1075	5.52	27	7.14
Non-major bleed	1042	4.39	141	3.96	881	4.46	20	5.14
Major bleed	354	1.4	98	2.67	247	1.17	9	2.16
Stroke/TIA	154	0.6	28	0.74	116	0.54	10	2.37
Recurrent VTE[b]	843	3.45	152	4.3	666	3.25	25	6.26
Hospital admission	2359	10.71	552	18.22	1750	9.38	57	16.42
MI	128	0.5	23	0.61	97	0.45	8	1.89
DVT event	605	2.44	111	3.09	475	2.28	19	4.67
PE event	304	1.2	54	1.46	243	1.15	7	1.67

Patients with missing treatment information were excluded from this analysis.
DVT = deep vein thrombosis, MI = myocardial infarction, (O)AC = (oral) anticoagulant, PAR = parenteral therapy, TIA = transient ischemic attack, VTE = venous thromboembolism.
[a] Only cancer events that were diagnosed >30 days from VTE diagnosis date are considered cancer endpoints.
[b] Some recurrent VTEs were both PEs and DVT, therefore they are counted as both DVT events and PE events.

4. Discussion

This observational study yielded some interesting findings. Firstly, the highest incidence of outcome events took place within the first 12 months. The incidence of all-cause mortality, recurrent VTE and major bleeding decreased after 36 months of follow-up as compared to the incidence rates at 24 and 12 months; the highest incidence of these events taking place was in the first 12 months, particularly the first month. The rates of new cancer, stroke/TIA and MI were also higher at 12 months than at 24 or 36 months. These findings are consistent with previous reports [3,13,14].

When comparing these findings to other registries such as the PREFER in VTE, which followed patients with acute VTE for a 12-month period, similar incidences of events such as all-cause mortality, recurrent VTE, major bleeding, non-major bleeding, and stroke/TIA were observed after this time point. Understandably, fewer patients in the PREFER in VTE registry were treated with DOACs across all countries since DOACs at that time were only launched in DACH regions, but when excluding patients from non-DOAC launched countries, a similar trend was observed over 12 months, where there was a large reduction in the proportion of patients treated with heparin and a steep increase in the proportion of patients treated with DOACs [14]. In the RIETE registry, where follow-up data was limited to 90 days, similar trends in events such as major bleeding and VTE recurrence were also seen [15].

What this shows is that GARFIELD-VTE is complementary to and builds upon the current data that is available on clinical outcomes in VTE, highlighting that the highest incidence of events occurs in the first 12 months. These findings emphasise the clinical importance of providing optimal treatment soon after diagnosis.

Approximately one-third of major bleeds at 36 months were localized to the upper or lower GI tract. This finding is consistent with what was seen at 12 months and supports the concept that the GI tract is the most common site of bleeding in patients receiving AC [16]. Almost two thirds of all episodes of recurrent VTE presented as DVTs alone, with the remainder being PE with or without associated DVT. It should also be noted that a small proportion of patients experienced a second major bleed or recurrent VTE event, which could have potentially affected their treatment regimen and/or risk of other events, however any further analysis of this was beyond the scope of the study.

The proportion of patients who died from VTE or bleeding in this registry was small (<11 % in total). It should be noted, however, that there may be patients in whom PE as a cause of death could not be ruled out, such as patients with sudden death. In many randomized trials of VTE treatment, such deaths were classified as PE deaths. Some of the risk factors of VTE could have been identified pre-diagnosis. This study highlights the importance of preventative strategies such as conducting a robust risk assessment before elective and emergency surgery admissions and appropriate thromboprophylaxis for high-risk patients [17].

When comparing event rates of patients on different treatments, those treated with OAC had a lower rate of all-cause mortality, major bleeding, and recurrent VTE compared to patients treated with PAR or no OAC. Although these findings are consistent with that observed in long-term safety trials of OACs [18] they have not been reflected in such a large global observational registry and provide supportive real-world evidence of the long-term safety of OAC treatment in patients with VTE. It should also be noted that typically those that are treated with PAR would be cancer patients, so this could explain the higher rate of all-cause mortality.

VTE is a multifaceted disease and shares many risk factors with ischemic stroke and myocardial infarction, such as hypertension, obesity, dyslipidaemia, diabetes and immobilization [19]. This association was first suggested in 2003, where the presence of a carotid artery plaque was shown to increase the risk of VTE by more than two fold [20]. Although the observed incidence of arterial events was relatively low in GARFIELD-VTE, evidence suggests that VTE overlaps in etiology and pathophysiology with coronary artery disease, and clinicians should always consider the same cardiovascular risk reduction strategies for the prevention of VTE [21].

Both in this registry and in others, mortality rates were higher than those in randomized clinical trials (RCTs), likely reflecting the stringent inclusion and exclusion criteria for patient selection in the RCTs [5–8] and the smaller proportion of patients with cancer.

Many of the strengths of the GARFIELD-VTE registry have been previously published, however some points worth reinterring is that the GARFIELD-VTE protocol mandated that 10 % of all eCRFs are verified with source documentation to ensure a high quality of data. This registry also required investigators to be educated in advance about methods of patient screening, enrolment, and appropriate follow-up procedures.

Due to the observational nature of registries, GARFIELD-VTE is subject to limitations, including collection of non-randomized data, incomplete data collection and the lack of centrally adjudicated outcomes. The presence of missing data is not surprising given the random selection of sites, some of which have minimal clinical research experience, however, the proportion of missing data is small. It should also be

considered that the treatment duration of anticoagulants and ultimately, patient outcomes may be influenced by whether the patients has any transient or persistent risk factors. Current guidelines recommend anticoagulation treatment for 3 months after VTE caused by transient risk factors, and longer if caused by persistent risk factors. A separate analysis, comparing 1-year outcomes in patients with transient provoking factors and unprovoked factors in the GARFIELD-VTE registry has already been published and showed that event rates of recurrent VTE and major bleeding were comparable between groups [22], however this comparison was not conducted in this analysis.

Despite these limitations, it is important to note that prospective registries, compared to retrospective cohort or chart review studies are usually considered to be of higher quality evidence. The key reasons for this may be that when a study is designed prospectively, clear research questions have already been defined and recall bias is limited, which is a feature typically associated with retrospective studies such as case control studies. Unlike retrospective studies using electronic health records, the data are recorded according to physician and study nurse knowledge of the patient plus the patient record, not just the mapping of patient codes such as ICD-10 or CPT codes. The prospective nature of this study also means that it was possible to estimate the population at risk of key outcomes such as recurrent VTE, major bleeding and all-cause mortality [23] .

In summary, this study provides a global perspective of patient outcomes 36 months after the diagnosis of VTE and provides a framework for future VTE studies. The high rates of death, recurrent VTE and bleeding in the first year after VTE diagnosis, particularly in the first month, highlights the importance of swift and effective VTE treatment in newly diagnosed patients. When comparing outcomes of difference treatments, the low event rates of mortality, major bleeding, and recurrent VTE seen in patients treated with OAC versus PAR and no OAC further supports their long-term safety in a real-word setting.

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Appendix A

Appendix Table A1
Site of Non-major bleeds. The data are the occurrence and percent of patients with a Non-major bleed during that time period.

Site of major bleed	12 months (N = 821)	36 months (N = 1053)
Intra-spinal	0 (0.0)	0 (0.0)
Intra-ocular/retinal	0 (0.0)	0 (0.0)
GI upper	25 (3)	32 (3)
GI lower	96 (11.7)	126 (12)
Macroscopic haematuria	114 (13.9)	143 (13.6)
Abnormal uterine (metorrhagia)	35 (4.3)	43 (4.1)
Menorrhagia	89 (10.8)	94 (8.9)
Intra-articular	0 (0.0)	0 (0.0)
Intra-muscular (no compartment syndrome)	15 (1.8)	21 (2)
Intra-muscular (with compartment syndrome)	0 (0.0)	0 (0.0)
Epistaxis	140 (17.1)	179 (17)
Gingival	44 (5.4)	54 (5.1)
Intra peritoneal	1 (0.1)	2 (0.2)
Retro-peritoneal	0 (0.0)	0 (0.0)
Puncture site	20 (2.4)	26 (2.5)

(*continued on next page*)

Appendix Table A1 (*continued*)

Site of major bleed	12 months (N = 821)	36 months (N = 1053)
Skin (ecchymosis other than puncture site)	86 (10.5)	121 (11.5)
Haemoptysis	34 (4.1)	48 (4.6)
Haemopericardium	0 (0.0)	0 (0.0)
Haemothorax	2 (0.2)	3 (0.3)
Haemorrhagic stroke	0 (0.0)	0 (0.0)
Other	96 (11.7)	135 (12.8)
Unknown	9 (1.1)	9 (0.9)

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