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ORIGINAL ARTICLE

Management strategies and clinical outcomes in patients with inferior vena cava thrombosis: Data from GARFIELD-VTE

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Abstract

Background: Inferior vena cava (IVC) thrombosis is a rare form of venous thromboembolism (VTE). The optimal treatment strategies and outcomes are unclear in patients with this presentation.

Objective: We aimed to compare baseline characteristics, treatment patterns and 24-month outcomes in IVC thrombosis patients ($n = 100$) with lower extremity deep vein thrombosis (LEDVT) patients ($n = 7629$).

*A full list of investigators is given in the Supplemental Materials.

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Methods: GARFIELD–VTE is a prospective, observational registry of 10 868 patients with objectively diagnosed VTE from 415 sites in 28 countries.

Results: IVC thrombosis patients were younger (51.9 vs. 59.8 years), more frequently had active cancer (26.0% vs. 8.9%) or history of cancer (21.0% vs. 12.2%), and less frequently had recent trauma or surgery than LEDVT patients. IVC thrombosis was more frequently treated with parenteral anticoagulants alone (35.1% vs. 15.9%), whereas patients with LEDVT more commonly received vitamin K antagonists (32.0% vs. 25.8%) or direct oral anticoagulants (49.0% vs. 35.1%). Thrombolysis (11.0% vs. 3.6%) and surgical/mechanical interventions (4.0% vs. 1.4%) were more frequent in IVC thrombosis. At 24-months, the rate per 100 person-years (95% confidence interval) of all-cause mortality was higher in patients with IVC thrombosis than LEDVT (13.28 [8.57–20.58] vs. 4.91 [4.55–5.3]); the incidence of cancer-associated mortality was comparable as was the incidence of VTE recurrence (4.11 [1.85–9.15] vs. 4.18 [3.84–4.55]). Major bleeding was slightly higher in IVC thrombosis (2.03 [0.66–6.31] vs. 1.66 [1.45–1.89]).

Conclusion: In summary, IVC thrombosis patients have higher all-cause mortality rates than those with LEDVT, a finding only partly attributable to malignancy.

KEYWORDS

anticoagulation, deep vein thrombosis, inferior vena cava thrombosis, pulmonary embolism, venous thromboembolism

1 | INTRODUCTION

Venous thromboembolism (VTE) is a common and major public health problem, associated with significant morbidity, mortality, and healthcare costs.[1] While reported incidence rates for pulmonary embolism (PE) and deep vein thrombosis of the lower extremity (LEDVT) range from 29 to 78 and 45 to 117 per 100 000 person-years, respectively,[1-3] thrombosis of the inferior vena cava (IVC) remains an under-recognized entity.[4]

In a population-based study, the reported incidence of IVC thrombosis was 2.82% of all LEDVT.[5] IVC thrombosis occurs most commonly with proximal extension of LEDVT, but it may occur in isolation in patients with cancer or in those with IVC atresia or other IVC abnormalities. Heritable or acquired hypercoagulable states increase the risk of IVC thrombosis.[6,7]

The optimal treatment and outcomes of IVC thrombosis are uncertain as there are currently no specific guidelines or recommendations for treating these patients. Data from randomized controlled trials are limited because IVC thrombosis was not classified as a distinct entity. Anticoagulation is the mainstay of treatment for IVC thrombosis; catheter-directed thrombolysis or pharmaco-mechanical catheter-directed thrombolysis should be considered in selected patients.[6-11] Long-term outcomes of patients with IVC thrombosis have not been reported.

To address these gaps in knowledge, we used data from the Global Anticoagulant Registry in the FIELD (GARFIELD)-VTE (ClinicalTrials.gov identifier: NCT02155491); a prospective, non-interventional observational study of 10 868 patients with objectively diagnosed VTE from 415 sites in 28 countries.[12] We compared baseline characteristics, treatment patterns and 24-month outcomes in patients with IVC thrombosis with or without associated pulmonary embolism (PE) with those in patients with LEDVT alone with or without associated PE.

Essentials

- IVC thrombosis is rare and thus optimal treatment strategies and outcomes are unclear.
- We investigated treatment patterns and 2-year outcomes in patients with IVC thrombosis compared to LEDVT.
- IVC thrombosis patients are typically treated according to current international guidelines and recommendations for VTE management.
- IVC thrombosis patients have an increased risk of mortality in comparison to patients with LEDVT, only partly attributable to malignancy.

2 | METHODS

2.1 | Study design and participants

The rationale and design of the GARFIELD-VTE registry has been previously reported.[12] Patients were prospectively and consecutively enrolled over 3 years into two separate cohorts. Men and women aged ≥18 years with an objectively confirmed diagnosis of symptomatic VTE

within 30 days of entry into the registry were eligible for inclusion in this study. The study excluded patients with superficial vein thrombosis, those participating in an interventional study that dictates treatments, or those for whom long-term follow up was not possible. The aim of the registry is to record standard local practices. Therefore, no specific treatments, tests or procedures are mandated by the protocol. Decisions to initiate, continue, or change treatment were solely at the discretion of the treating physicians and their patients. Individual participant data collected for the study are not available to others.

2.2 | Selection of study sites

The national coordinating investigators identified the care settings they believed most accurately represented the management of VTE patients in their country. The contract research organization provided a list of sites that reflected these care settings, from which study sites were computationally selected at random. Sites that agreed to participate were recruited after a qualification telephone call, and all investigators completed an educational program providing guidance on patient screening, enrolment, and follow-up in the registry.

2.3 | Data collection

Data were collected by treating physicians by means of 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, which was responsible for checking the completeness and accuracy of data collected from medical records. Patients were assigned a unique identifier and identifiable data were removed at the hospital source to ensure confidentiality. The GARFIELD-VTE protocol mandates (a) centralized auditing of 10% of all eCRFs by comparison with source documentation, (b) provision of electronic audit trails for all data modifications, and (c) subjecting critical variables to additional audit. This study reports prospectively collected data from patients enrolled from 12 May 2014 to 4 January 2017. The data were extracted from the study database in October 2020.

2.4 | Clinical outcomes

Outcomes were recorded in standardized eCRFs. The primary clinical outcomes were all-cause mortality, recurrent VTE, and major bleeding. Major bleeding was defined as clinically overt bleeding associated with a critical site (e.g., intracranial, intraspinal, intraocular), decrease in hemoglobin of ≥2 g/dl, transfusion of ≥2 units of packed red blood cells, or a fatal outcome.[13] Non-major bleeding was defined as any episode of overt bleeding not meeting the criteria for major bleeding.[14] Recurrent VTE was characterized as any new VTE following the initial VTE diagnosis, and patients with recurrent VTE must have completed treatment for the previous event. The rates of hospitalization, bleeding, cancer, stroke/transient ischemic attack, and myocardial infarction were also recorded. Additionally, information was collected regarding the cause of death and nature of bleeding. Cancer that was diagnosed more than 30 days after the VTE diagnosis date was considered as a cancer endpoint. Patients were characterized as having active cancer if they were diagnosed and/or receiving treatment for their cancer during the window of ≤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.[15] For all other outcomes, events that occurred from the day of diagnosis onward were considered outcomes. Only the first occurrence of each event type was considered. Outcomes were not centrally adjudicated.

2.5 | Ethics statement

The registry is conducted in accordance with the Declaration of Helsinki and guidelines from the International Conference on Harmonization on Good Clinical Practice and Good Pharmacoepidemiological Practice and adheres to all applicable national laws and regulations. Independent ethics committees for each participating country and the hospital-based institutional review boards approved the design of the registry. All patients provided written informed consent to participate. Confidentiality and anonymity of patients recruited into this registry are maintained.

2.6 | Statistical analyses

This study focused on post-hoc analysis of patients with a confirmed diagnosis of IVC thrombosis with or without concurrent PE. These patients were descriptively compared with patients with a confirmed diagnosis of LEDVT with or without PE. Patients without an objectively confirmed diagnosis of VTE, patients with upper extremity DVT, superior vena cava thrombosis or other unusual sites of DVT were excluded from the analysis. Continuous variables are summarized as means (standard deviation), and categorical variables are presented as frequency and percentage. Unadjusted event rates and the associated 95% confidence interval (CI) were estimated using Poisson regression and are expressed per 100-person years. Patients with missing values were not removed from the study (available case analysis). Statistical analyses were conducted using R statistical software version 3.6.1 (R Development Core Team) and SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA). In all cases, the threshold for assessing statistical significance for two-sided tests was set at level $\alpha = .05$.

2.7 | Data sharing

For original data, please contact Dr. Saverio Virdone (SVirdone@tri-london.ac.uk).

3 | RESULTS

3.1 | Baseline demographics & diagnosis

Of the total 10 868 available patients, 7729 patients were eligible for analysis. Of these, 100 patients (1.3%) were classified as having IVC thrombosis (with or without PE), and 7629 (98.7%) were classified as having LEDVT (with or without PE) (Figure 1). Among patients with LEDVT, 6071 (79.6%) had LEDVT alone and 1558 (20.4%) had both LEDVT and concurrent PE. Of the 100 patients with IVC thrombosis, 12 (12.0%) were diagnosed with concurrent PE. Compression ultrasonography was used to confirm the diagnosis in 66.0% of patients with IVC thrombosis and in 96.2% of patients with LEDVT. Computed tomography (CT) venography or contrast venography was used more commonly to establish the diagnosis in patients with IVC thrombosis than in those with LEDVT (48.0% and 4.3%, respectively vs. 10.0% and 1.3%, respectively) (Table S1).

The median age of patients with IVC thrombosis was lower than that of patients with LEDVT (median age 51.9 years vs. 59.8 years) (Table 1). Of patients with IVC thrombosis, 45.0% were <50 years old compared with 31.9% of patients with LEDVT. Gender distribution was comparable between the two groups (47.0% vs 50.9% male, respectively). Median follow up times are shown in Table S2.

Active cancer and history of cancer were more frequently reported in patients with IVC thrombosis (26.0% and 21.0%, respectively) than in those with LEDVT (8.9% and 12.2%, respectively). A higher proportion of patients with IVC thrombosis had a history of recent hospitalization (15.0% vs. 11.2%, respectively), whereas a higher proportion of patients with LEDVT had a history of recent trauma of the lower limbs (9.4% vs. 2.0%), surgery (12.1% vs. 8.0%), a prior episode of VTE (16.2% vs. 10.0%) or a family history of VTE (6.3% vs. 2.0%, respectively). A comparison of provoking and predisposing risk factors is provided in Table 2.

3.2 | Treatment

Thrombolytic therapy was administered to 11.0% of patients with IVC thrombosis and to 3.6% of those with LEDVT. Surgical/mechanical interventions were also more common in patients with IVC thrombosis (4.0% vs. 1.4%, respectively).

After diagnosis, 98.1% of patients with IVC thrombosis and 97.9% of those with LEDVT were initiated on anticoagulant treatment (Figure 2). Patients with IVC thrombosis were more likely to receive parenteral anticoagulants alone (35.1% vs. 15.9%). In contrast, patients with LEDVT were more likely to receive parenteral therapy in combination with a VKA than patients with IVC thrombosis (26.1% vs. 18.6%) or to be given a direct oral anticoagulant (DOAC) alone (34.2% vs. 22.7%).

Patients with LEDVT and IVC thrombosis with concurrent cancer were most likely to receive parenteral anticoagulants (55.4% and 79.2%, respectively), however VKA and DOAC usage was higher in LEDVT patients with concurrent cancer (17.8% and 26.8%) than in IVC thrombosis patients with concurrent cancer (12.5% and 8.3%).

At 3-, 6-, 12, and 24-months, the proportions of patients with IVC thrombosis still receiving anticoagulant treatment were 81.4%, 69.1%, 46.3%, and 38.2% respectively, compared with 87.1%, 72.0%, 53.4%, and 45.2% of patients with LEDVT (Figure 2).

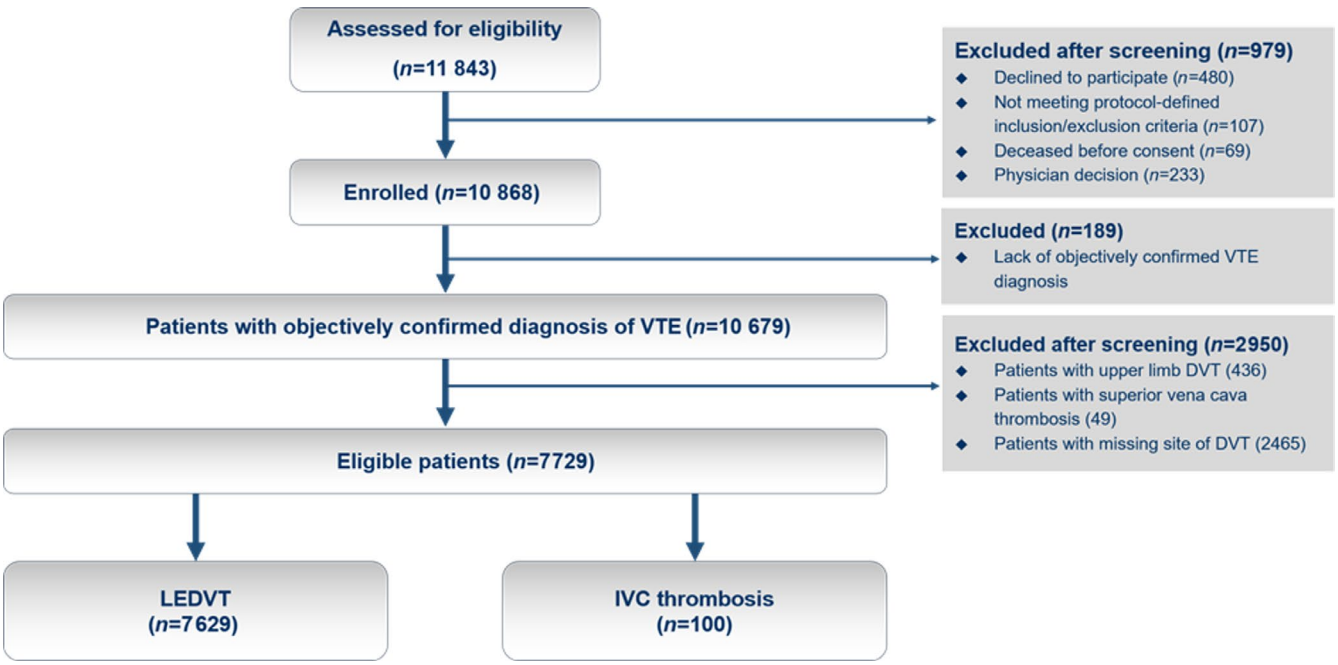

FIGURE 1 Study population flowchart. DVT, deep vein thrombosis; IVC, inferior vena cava; LEDVT, lower extremity deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism

TABLE 1 Baseline characteristics and care settings

Variable	LEDVT ($n = 7629$)	IVC thrombosis ($n = 100$)
Male, *n* (%)	3881 (50.9)	47 (47.0)
Age, median years (IQR)	59.8 (45.9–71.2)	51.9 (39.1–67.6)
Age groups, *n* (%)		
<50	2436 (31.9)	45 (45.0)
50–65	2279 (29.9)	24 (24.0)
65–75	1581 (20.7)	19 (19.0)
75–85	1052 (13.8)	10 (10.0)
>85	281 (3.7)	2 (2.0)
BMI, kg/m^2, median (IQR)	27.3 (24.1–31.2)	26.5 (22.5–30.5)
Min–Max	12.5–80.0	15.9–46.2
Missing data	753	6
Care setting, *n* (%)		
Hospital	5332 (69.9)	82 (82.0%)
Outpatient setting	2297 (30.1)	18 (18.0%)
Specialty, *n* (%)		
Vascular medicine	4006 (52.5)	43 (43.0)
General practitioner	251 (3.3)	5 (5.0)
Internal medicine (Hematology and Intensive Care)	2799 (36.7)	38 (38.0)
Emergency medicine	181 (2.4)	1 (1.0)
Cardiology	391 (5.1)	13 (13.0)
Missing	1	0

Abbreviations: BMI, body mass index; CT, computed tomography; DVT, deep vein thrombosis; IQR, interquartile range; IVC, inferior vena cava; LEDVT, lower extremity DVT; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism.

3.3 | Clinical outcomes

At 24-months after VTE diagnosis, the unadjusted rate of all-cause mortality was higher in patients with IVC thrombosis than in those with LEDVT; 13.28 (95% CI, 8.57–20.58) vs. 4.91 (95% CI, 4.55–5.3) per 100 person-years, respectively (Table 3). The Kaplan-Meier survival curves are presented in Figure 3. Mortality was attributed to cancer in 57.1% of patients with IVC thrombosis and in 51.0% of those with LEDVT (Table S3). The incidence rates of VTE recurrence in patients with IVC thrombosis or LEDVT were comparable; 4.11 (95% CI, 1.85–9.15) vs. 4.18 (95% CI, 3.84–4.55) per 100 person-years, respectively. The incidence rate of major bleeding was slightly higher in IVC thrombosis compared to LEDVT; 2.03 (95%CI, 0.66–6.31) vs. 1.66 (95%CI, 1.45–1.89) per 100 person-years, respectively (Table 3). IVC thrombosis patients with active cancer had higher mortality, VTE recurrence and bleeding rates than IVC thrombosis patients without active cancer (Tables S4). IVC thrombosis patients with active cancer appear to have higher mortality than LEDVT patients with active cancer (Tables S5), however, the small number of events does not allow for further statistical analysis.

TABLE 2 History of provoking risk factors within 3 months prior to diagnosis of VTE

	LEDVT ($n = 7629$)	IVC thrombosis ($n = 100$)
Persistent provoking factors, *n* (%)		
Active cancer[a]	681 (8.9)	26 (26.0)
Transient provoking factors, *n* (%)		
Acute medical illness	428 (5.6)	4 (4.0)
Hospitalization	854 (11.2)	15 (15.0)
Long-haul travelling	367 (4.8)	2 (2.0)
Surgery	926 (12.1)	8 (8.0)
Trauma of the lower limb	715 (9.4)	2 (2.0)
Hormone replacement therapy (females)	123 (1.6)	0 (0.0)
Oral contraception (females)	383 (5.0)	5 (5.0)
IVC filter inserted at baseline	129 (1.7)	4 (4.0)
IVC filter inserted prior to VTE diagnosis	6 (0.1)	2 (2.0)
Predisposing risk factors, *n* (%)		
Chronic heart failure	202 (2.7)	3 (3.0)
Chronic immobilization	447 (5.9)	6 (6.0)
Family history of VTE	479 (6.3)	2 (2.0)
History of cancer[b]	932 (12.2)	21 (21.0)
Known thrombophilia	242 (3.2)	3 (3.0)
Prior VTE[c]	1233 (16.2)	10 (10.0)

Abbreviations: DVT, deep vein thrombosis; IVC, inferior vena cava; LEDVT, lower extremity DVT; PE, pulmonary embolism; VTE, venous thromboembolism.

[a]Active cancer: diagnosis and/or active cancer treatment ≤90 days before and up to 30 days after VTE diagnosis.

[b]History of cancer: remission of cancer or active cancer treatment >90 days prior to VTE diagnosis.

[c]Prior VTE: VTE for which prior treatment had been completed.

4 | DISCUSSION

This prospective, observational study investigated clinical characteristics, management strategies, and 24-month outcomes in a cohort of patients with IVC thrombosis captured in the global GARFIELD-VTE registry and compared them with those of patients with LEDVT without IVC thrombosis.

Patients with IVC thrombosis were younger than those with LEDVT, perhaps explained by the possible existence of vascular anomalies in those with IVC thrombosis which led to VTE at an earlier age. Congenital IVC anomalies are rare with a prevalence of 0.6% in individuals with congenital heart disease and 0.3% in healthy individuals.[16,17] Nevertheless, they are associated with an increased risk of VTE with a rate of over 60%.[18,19] These anomalies have a male predominance, and usually present in the third or fourth decade of life.[20-22] The May-Thurner Syndrome (MTS) is another anatomical

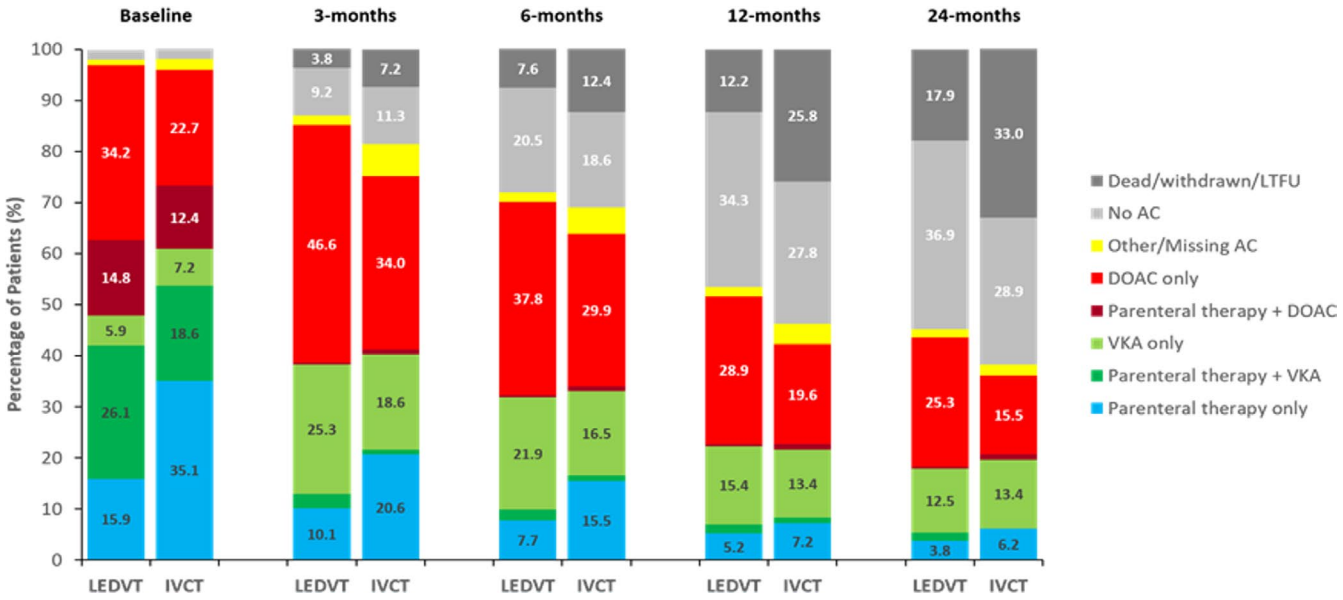

FIGURE 2 Anticoagulation treatment patterns over 24-months follow up. AC, anticoagulation; DOAC, direct oral anticoagulant; IVCT, inferior vena cava thrombosis; LEDVT, lower extremity deep vein thrombosis; LTFU, lost to follow up; PE, pulmonary embolism; VKA, vitamin K antagonist

TABLE 3 Unadjusted 24-month annual incidence rate (per 100 person-years)

	LEDVT ($n = 7629$)		IVC thrombosis ($n = 100$)	
Event	*n*	Event rate (95% CI)	*n*	Event rate (95% CI)
All-cause mortality	652	4.91 (4.55–5.30)	20	13.28 (8.57–20.58)
Recurrent VTE	530	4.18 (3.84–4.55)	6	4.11 (1.85–9.15)
Recurrent DVT	407	3.17 (2.88–3.50)	5	3.42 (1.42–8.21)
Recurrent PE	151	1.15 (0.98–1.35)	1	0.67 (0.09)
Major Bleeding	217	1.66 (1.45–1.89)	3	2.03 (0.66–6.31)
Any bleeding	828	6.78 (6.31–7.23)	9	6.36 (3.31–12.23)
MI/ACS	54	0.41 (0.31–0.54)	1	0.67 (0.09–4.77)
Stroke/TIA	78	0.59 (0.47–0.74)	0	0.0 (0.0–∞)

Abbreviations: ACS, acute coronary syndrome; CI, confidence interval; LEDVT, lower extremity deep vein thrombosis; MI, myocardial infarction; PE, pulmonary embolism; TIA, transient ischemic attack; VTE, venous thromboembolism.

abnormality, where chronic compression of the left common iliac vein by an overlying right common iliac artery causes venous stasis, chronic intraluminal damage and a predisposition to DVT at a young age. There is no consensus on the management of MTS, however treatment by angioplasty with stenting is often required in addition to anticoagulation to prevent DVT recurrence.[23-25] Unfortunately, data regarding caval and iliac vein anatomy are unavailable in our database, however, it should be noted that in the group with IVC thrombosis, 45% of patients were under 50 years of age. In patients with IVC thrombosis, the proportion with a history of recent trauma to the lower limbs, or surgery, is lower than that in patients with LEDVT alone. This is of interest because aside from anatomical anomalies, risk factors for IVC thrombosis have not been previously described.

A few patients had IVC filter inserted either prior to or following VTE diagnosis. Notably, guidelines discourage routine placement of an IVC filter in VTE patients who are being treated with therapeutic anticoagulation while insertion of a retrievable IVC filter should be considered in selected patients with acute VTE and a contraindication to anticoagulant treatment.[26,27] The small numbers of patients who had IVC filter placed and missing data on retrieval times preclude further analysis with regards to the use of IVC filters in the context of IVC thrombosis.

Active cancer and history of cancer were more frequently reported in patients with IVC thrombosis. Cancer leads to an aggressive and extended thrombosis, and bilateral DVT at presentation has been consistently reported in patients with cancer.[28-31] Due to eCRF restrictions, data on concurrent IVC thrombosis and bilateral

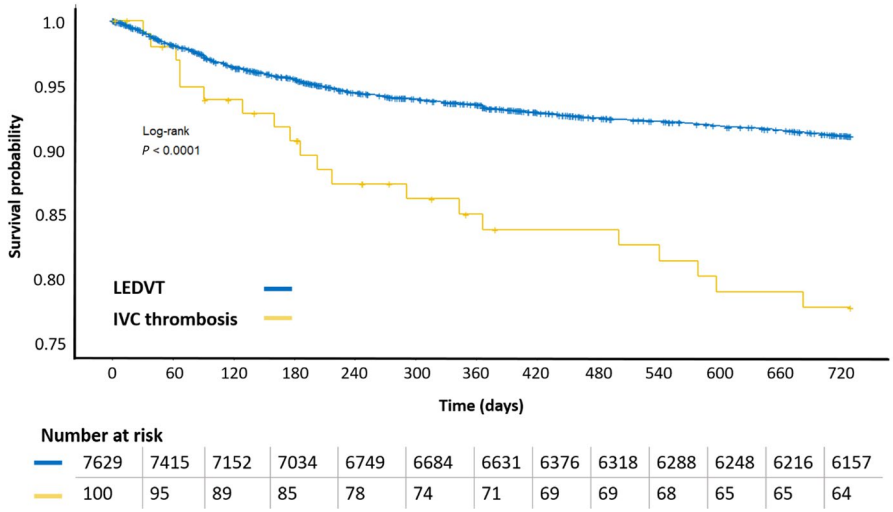

FIGURE 3 A Kaplan-Meier survival estimator for patients with IVC thrombosis vs. patients with LEDVT (with or without PE) without IVC thrombosis. DVT, deep vein thrombosis; IVC, inferior vena cava; LEDVT, lower extremity DVT

LEDVT are unavailable, however, involvement of the IVC may provide further support of the severe hypercoagulability associated with malignancy.[32,33]

Like patients with LEDVT, most patients with IVC thrombosis were given anticoagulant treatment. However, patients with IVC thrombosis were more likely to receive parenteral therapy alone and less likely to receive DOACs. This may be explained by the higher prevalence of cancer in the IVC thrombosis group because up until July 2018, guidelines recommended low-molecular-weight heparin for the treatment of cancer-associated VTE.[3] Certainly, IVC thrombosis patients with concurrent cancer were far more likely to receive parenteral therapy. Alternatively, the extent of the thrombosis and the limited evidence supporting the use of DOACs in the setting of IVC thrombosis may have prompted the preference for low molecular weight heparin over DOACs or VKAs.

Patients with IVC thrombosis had a significantly higher 24-month all-cause mortality rate than those with LEDVT. Analysis of causes of mortality suggests that this reflects only a slightly higher proportion of cancer-related deaths, and notably, a higher proportion of VTE-related deaths. Despite the small number of patients with IVC thrombosis, this finding suggests a need for additional research into the treatment of this condition. In this study, a higher proportion of patients with IVC thrombosis than with LEDVT alone underwent thrombolysis and/or surgical/mechanical interventions. The majority of patients with IVC thrombosis, however, were treated conservatively with anticoagulation alone, and no differences in the risks of VTE recurrence were observed. Despite this, patients with IVC thrombosis had a slightly higher risk of major bleeding than those with LEDVT alone. Because of the small numbers, impact of thrombolysis and surgical mechanical interventions on outcomes could not be explored.

IVC thrombosis comprised 1.3% of VTE in this cohort (exclusive of upper extremity DVT, superior vena cava thrombosis and other unusual sites of DVT), which is marginally lower than in previous reports.[5,34] This may be attributable to GARFIELD-VTE being a registry of symptomatic patients; asymptomatic IVC thrombosis patients may therefore be underrepresented in this study. Nonetheless, IVC thrombosis is unlikely to be asymptomatic in many patients.

In the only previous large report dedicated to IVC thrombosis patients, Alkhouli and colleagues reported short term outcomes documented within the Nationwide Inpatient Sample database, where a considerably higher proportion of patients were treated with catheter-directed thrombolysis, balloon angioplasty and stenting. When compared to propensity matched patients treated with anticoagulation alone, patients treated with catheter-directed thrombolysis had higher rates of in-hospital PE (OR 1.62, 95% CI 1.08–2.41, $p = .02$). In-hospital mortality, however, did not significantly differ between the two groups (OR 1.38, 95% CI 0.55–3.46, $p = .49$).[35] Longer term outcomes were not reported.

Our study has strengths and limitation. The strengths include the prospective design, the large size of the cohort of patients with objectively diagnosed VTE, and the high rate of successful follow up. Limitations include the lack of central adjudication of index events and outcomes, the small number of patients with IVC thrombosis relative to those with LEDVT, and the unavailability of information regarding thrombus burden. This is not surprising however, because of the rarity of IVC thrombosis. Furthermore, due to eCRF restrictions, reporting of the site of thrombosis precludes reporting on concurrent IVC thrombosis and LEDVT. Therefore, we are unable to ascertain the proportion of IVC thrombosis patients who had concurrent LEDVT. Finally, this study was not powered to compare various management strategies for IVC thrombosis, placement of IVC filters or associated congenital vascular anomalies.

In conclusion, we described current management strategies and clinical outcomes of patients with IVC thrombosis captured in the GARFIELD-VTE registry. Patients with IVC thrombosis are generally treated according to international practice guidelines for VTE.[2,3,27] Nevertheless, the all-cause mortality rate is higher in patients with IVC thrombosis than in those with LEDVT, which appears to be partly attributable to underlying malignancy. Future research is required to further elaborate systemic risk factors for IVC thrombosis, rates of post-thrombotic syndrome and the comparative effectiveness of low molecular weight heparin and DOACs.

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CONFLICT OF INTEREST

Omri Cohen: Research support from Pfizer. Walter Ageno: Honoraria from Boehringer Ingelheim, Bayer Pharma AG, Bristol Myers Squibb, Pfizer, Daiichi-Sankyo, Portola, Aspen, Sanofi. Alexander G. G. Turpie: Personal fees from Bayer Pharma AG and Janssen. Jeffrey I. Weitz: Research support from Canadian Institutes of Health Research, Heart and Stroke Foundation, and the Canadian Fund for Innovation. Honoraria from Bayer Pharma AG, Boehringer-Ingelheim, Bristol Myers Squibb, Daiichi-Sankyo, Ionis, Janssen, Merck, Portola, Pfizer, Servier, Novartis, Anthos, and Tetherex. Sylvia Haas: Honoraria from Aspen, Bayer Pharma AG, Bristol Myers Squibb, Daiichi-Sankyo, Pfizer, Portola, Sanofi. Shinya Goto: Research funding from Ono, Bristol Myers Squibb, Sanofi, and Pfizer. Personal fees from Thrombosis Research Institute and the American Heart Association. Samuel Z. Goldhaber: Research Support from Bayer Pharma AG, Boehringer-Ingelheim, BMS, BTG EKOS, Daiichi, Janssen, NHLBI, Thrombosis Research Institute. Consultancy fees from Bayer Pharma AG, Boehringer-Ingelheim. Harry Gibbs: declares personal fees from Pfizer, Bayer, Boehringer Ingelheim. Peter MacCallum: Honoraria from Bayer Pharma AG and Portolo. Sebastian Schellong: Speaker fees from Bayer Pharma AG, Boehringer-Ingelheim, Bristol Meyer Squibb, Daiichi-Sankyo, Sanofi Aventis and Pfizer. Consultancy fees from Bayer Pharma AG, Boehringer-Ingelheim, Daiichi-Sankyo, Sanofi Aventis, Aspen and Pfizer. Henri Bounameaux: Honoraria from Bayer Pharma AG. Lorenzo Mantovani: Grants from the Italian Ministry of Health-Ricerca Corrents- IRCCS Multimedica during the conduct of the study and grants and personal fees from Bayer Pharma AG, Boehringer-Ingelheim and Daiichi-Sankyo and personal fees from Pfizer outside the study. Paolo Prandoni: Personal fees from Bayer Pharma AG, Pfizer, Daiichi-Sankyo and Sanofi. Professor Ajay K Kakkar: Research grants from Bayer Pharma AG and Sanofi. Personal fees from Bayer Pharma AG, Sanofi S.A., Janssen Pharma, Verseon, Pfizer, and Anthos Therapeutics. Alfredo Farjat, Pantep Angchaisuksiri, and Gloria Kayani declare that they have no conflicts of interest in the research.

AUTHOR CONTRIBUTIONS

W. Ageno, A. G. G. Turpie, J. I. Weitz, S. Haas, S. Goto, S. Z. Goldhaber, P. Angchaisuksiri, G. Kayani, S. Schellong, H. Bounameaux, L. G. Mantovani, P. Prandoni and A. K. Kakkar all contributed to the concept, design, and conduct of the study. A. E. Farjat conducted the statistical analysis. All authors contributed to data interpretation. O. Cohen wrote the manuscript. All authors critically reviewed the manuscripts. A. K. Kakkar and Gloria Kayani handled funding and supervised the registry.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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