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Profile of Patients with Isolated Distal Deep Vein Thrombosis versus Proximal Deep Vein Thrombosis or Pulmonary Embolism: RE-COVERY DVT/PE Study

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Abstract

Isolated distal deep vein thrombosis (IDDVT) is presumed to be more benign than proximal DVT (PDVT) or pulmonary embolism (PE), suggesting a need for different management approaches. This subgroup analysis of the RE-COVERY DVT/PE global, observational study investigated patient characteristics, hospitalization details, and anticoagulant therapy in patients with IDDVT in real-world settings in 34 countries enrolled from January 2016 to May 2017. Data were analyzed descriptively according to the type and location of the index venous thromboembolism (VTE): IDDVT, PDVT ± distal DVT (DDVT), and PE ± DVT. Of the 6,095 eligible patients, 323 with DVT located outside the lower limb and no PE were excluded. Of the remaining 5,772 patients, 17.6% had IDDVT, 39.9% had PDVT ± DDVT, and 42.5% had PE ± DVT. IDDVT patients were younger and had fewer risk factors for VTE than the other groups. Other comorbidities were less frequent in the IDDVT group, except for varicose veins, superficial thrombophlebitis, and venous insufficiency. IDDVT patients were less likely to be diagnosed in an emergency department (22.3 vs. 29.7% for PDVT ± DDVT and

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45.4% for PE ± DVT) or hospitalized for VTE (29.2 vs. 48.5% for PDVT ± DDVT and 75.0% for PE ± DVT). At hospital discharge or 14 days after diagnosis (whichever was later), non–vitamin K antagonist oral anticoagulants were the most commonly used anticoagulants (55.6% for IDDVT, 54.7% for PDVT ± DDVT, and 52.8% for PE ± DVT). Although differences in patient characteristics, risk factors, and clinical management were identified, anticoagulant treatment of IDDVT was almost equal to that of PDVT or PE. Prospective studies should investigate whether, in a global perspective, this is an appropriate use of anticoagulants.

Venous thromboembolism (VTE) may be associated with significant morbidity, risk of recurrence, and fatality from pulmonary embolism (PE). Approximately two-thirds of patients present with deep vein thrombosis (DVT) and one-third with PE.[1] For those patients with proximal DVT (PDVT), anticoagulation is warranted to prevent clinical PE and postthrombotic syndrome. However, there is longstanding debate as to whether patients with isolated distal DVT (IDDVT) should be anticoagulated.[2–6] The decision to anticoagulate needs to balance the potential for IDDVT to extend to PDVT and PE against the increased risk of bleeding. Prospective and retrospective management trials[2,7] and literature analyses[4,8] indicate that only a minority (on average ~10 to 20%) of patients with IDDVT are at risk of developing PDVT and/or PE if left untreated. Therefore, anticoagulation may be unnecessary. Current guidelines suggest that patients with IDDVT who do not have severe symptoms or risk factors for progression may be monitored with serial imaging rather than treated with anticoagulation. For patients with severe symptoms or with risk factors that predispose to recurrent VTE (such as active cancer, previous VTE, or inpatient status), the use of anticoagulation for at least 3 months is suggested.[9,10] At present, there are no other reliable predictors that identify IDDVT patients at risk of progression to PDVT/PE.

The RE-COVERY DVT/PE study is a global prospective cohort study that aims to characterize patients who present with acute VTE in routine clinical practice.[11] In the primary analysis of the overall cohort, we characterized the DVT/PE patient population and explored anticoagulant use for the treatment of acute VTE. Overall, 77% of patients received oral anticoagulants (54% non–vitamin K antagonist oral anticoagulants [NOACs] and 23% vitamin K antagonists [VKAs]), with 20% receiving parenteral anticoagulation only; NOAC treatment was less frequent in patients with cancer, chronic renal disease, heart failure, or stroke.[12]

Despite current guidelines, studies have shown that anticoagulants are used in almost all patients with IDDVT.[13–16] The aim of this ancillary study of RE-COVERY DVT/PE was to further investigate the characteristics, management, and anticoagulant use in patients with IDDVT in clinical practice.

Methods

Study Design

RE-COVERY DVT/PE is a multicenter, international, observational study designed with two phases. Patients with acute DVT and/or PE were recruited from Europe, North America, Asia, the Middle East, and Latin America. The rationale and design of the study have been described elsewhere.[11] To minimize the risk of potential selection bias, in the first phase of the study, investigators were encouraged to include consecutive patients with acute VTE irrespective of initial treatment. As such, each patient presenting with a VTE was approached for study enrollment, irrespective of how they were treated and managed. Assessment of a patient for study participation was within 6 months after diagnosis of the acute VTE. Patients were eligible for inclusion if they were aged ≥18 years with an objective diagnosis of acute DVT and/or PE. The present subgroup analysis is based on the first phase. In the second phase, the safety and effectiveness of dabigatran and VKAs over a follow-up period of 1 year will be compared.

Study initiation required the approval of dabigatran for VTE in participating countries and a robust site feasibility process to ensure that participating sites represented the standard of care within that country. These sites included hospitals, outpatient care centers, anticoagulation clinics, and general/private practice offices. The study was performed in compliance with the protocol and the principles laid down in the Declaration of Helsinki and in accordance with the applicable sections of the guidelines for Good Clinical Practice, Good Epidemiological Practice, and Good Pharmacoepidemiology Practice, and local regulations. Written informed consent was provided by patients or their legal representatives in accordance with local regulations before entering the study.

Eligibility Criteria

Inpatients or outpatients aged ≥18 years with symptomatic, objectively diagnosed, acute DVT and/or PE were eligible for inclusion. Patients were excluded only if there was a need for anticoagulation for conditions other than VTE or current participation in another clinical trial for VTE.

Data Collection and Analysis

At the baseline visit, patient characteristics, as assessed by the investigator, and anticoagulant treatment administered following objective diagnosis of VTE were recorded. Investigators also recorded information about the index VTE event, including clinical signs and symptoms of VTE; type of objective testing used for VTE (venous compression ultrasonography, venography for DVT, or other examinations deemed relevant for

routine clinical practice for DVT diagnosis); and the resultant location, extent, and severity of venous thrombus. Baseline data were collected for the time of the index event based on assessment of the patient (e.g., patient symptom history), review of hospital/medical records, and available laboratory and diagnostic test reports. As parenteral anticoagulation with heparin or fondaparinux may have preceded treatment with oral anticoagulants, anticoagulant treatments were recorded again either at hospital discharge or 14 days after diagnosis, whichever was later. Adverse events occurring during this period were also recorded. A web-based electronic data system with secure access features captured all clinical data and site/investigator characteristics and maintained a complete electronic audit trail.

Baseline patient characteristics, details of hospitalization, and choice of anticoagulant therapy were tabulated for three groups of patients according to the type and location of their index VTE. These were distal lower extremity DVT (below the popliteal vein/trifurcation area), no iliac and/or proximal lower extremity DVT, and no PE (IDDVT only); iliac and/or proximal lower extremity DVT with or without distal lower extremity DVT, but no PE (PDVT ± distal deep vein thrombosis [DDVT]); and any PE with or without any DVT (PE ± DVT). Therapy at baseline and at 14 days or at discharge was recorded. The assignment of anticoagulant treatment choice for the current analysis was based on the therapy at hospital discharge or 14 days after diagnosis (whichever was later); as such, patients who received parenteral anticoagulation prior to or overlapping with oral anticoagulation were considered to be treated with the relevant oral anticoagulant. The number of patients with missing data for any parameter is included in percentage calculations and shown as a category or footnote. Due to the descriptive and exploratory nature of the study, no formal statistic testing was done. Instead, 95% confidence intervals were calculated around means (for continuous variables) and around percentages as Clopper–Pearson intervals (for discrete variables).[17]

Results

Baseline Patient Characteristics

Patients ($N = 6,194$) were consecutively enrolled from January 2016 to May 2017, from 229 sites in 34 countries (►**Table 1**) across Europe (59.4%), North America (15.9%), the Middle East/Turkey (11.0%), Asia (9.8%), and Latin America (3.9%). Of these, 6,095 patients were eligible for study entry. Ninety-nine enrolled patients were excluded owing to issues with informed consent form ($n = 29$), inclusion criteria not met (20), and exclusion criteria met (4); a further 46 patients had no documented VTE treatment (24 DVT, 19 PE, and 3 DVT and PE). These 46 patients (0.74% of the total enrolled) could not be categorized into any of the specified treatment sets and therefore were excluded. Of the 6,095 eligible patients, 323 who had DVT located outside the lower limb and no PE, were excluded, leaving 5,772 patients in this analysis. Most of the eligible patients were enrolled at hospital study sites (either

Table 1 Countries enrolling patients in the RE-COVERY DVT/PE study (total $N = 6,194$)

Region and country	Patients, *n* (%)	Region and country	Patients, *n* (%)
Europe	3,618 (59.4)	Middle East	668 (11.0)
Austria	188 (3.1)	Arab Emirates	2 (0.0)
Belgium	43 (0.7)	Egypt	13 (0.2)
Bulgaria	93 (1.5)	Lebanon	51 (0.8)
Czech Republic	255 (4.2)	Turkey	602 (9.9)
Germany	123 (2.0)	North America	970 (15.9)
Greece	106 (1.7)	Canada	319 (5.2)
Hungary	264 (4.3)	USA	651 (10.7)
Italy	297 (4.9)	Latin America	239 (3.9)
Latvia	9 (0.1)	Argentina	153 (2.5)
The Netherlands	54 (0.9)	Brazil	19 (0.3)
Poland	42 (0.7)	Chile	5 (0.1)
Portugal	57 (0.9)	Colombia	56 (0.9)
Romania	101 (1.7)	Mexico	2 (0.0)
Russian Federation	458 (7.5)	Peru	4 (0.1)
Serbia	502 (8.2)	Asia	600 (9.8)
Slovakia	169 (2.8)	Malaysia	44 (0.7)
Slovenia	23 (0.4)	Philippines	33 (0.5)
United Kingdom	834 (13.7)	South Korea	414 (6.8)
		Thailand	109 (1.8)

university/research hospitals [29.6%] or other hospitals [60.6%]) with the remainder in a clinic, practice, specialist office, or medical center (6.1%), or in primary care (3.7%).

Baseline demographic characteristics of all eligible patients are summarized in ►**Table 2**. The VTE index events were IDDVT in 17.6%, PDVT ± DDVT in 39.9%, and PE ± DVT in 42.5%. In the PDVT ± DDVT group, all patients had "proximal" and/or iliac DVT (per study definition), 15.4% had iliac vein DVT and 41.8% also had DDVT. Proximal DVT without iliac involvement comprised 96.6% of this group and iliac DVT without other proximal location comprised 0.4%. Among patients with PE ± DVT, the majority (64.8%) had PE alone; the remainder had PE plus any DVT, and for these patients ($n = 863$), locations were recorded as distal in 56.7%, proximal in 68.6%, and iliac vein in 9.5% (more than one location was possible).

Mean age was shown to be youngest in the IDDVT group (►**Table 2**). More patients with IDDVT were employed full time, and fewer were retired, compared with the other two groups. Mean calculated creatinine clearance was highest in the IDDVT group.

Patients with Caucasian ethnicity had a higher representation in the IDDVT and PDVT ± DDVT groups than in the PE ± DVT group (81.7 and 78.6% vs. 70.9%, respectively). In contrast, Asian and Black or African American patients had a lower representation in the IDDVT and PDVT ± DDVT groups than in the PE ± DVT group (10.0 and 8.8% vs. 13.5% for Asian patients; and 1.1 and 2.3% vs. 4.2% for Black or African American patients). To explore this in more detail, 19, 16, and 7% of Caucasians, Asians, and Black or African American patients had IDDVT, compared with 41, 32, and 32% with PDVT ± DDVT and 40, 52, and 62% with PE ± DVT, respectively. The ratio of IDDVT to PDVT was, therefore, relatively similar in patients who were Caucasian (0.46) and Asian (0.50), but notably lower in Black or African American patients (0.20).

Table 2 Baseline demographic characteristics

	Group A IDDVT[a] $N = 1,016$	**Group B PDVT ± DDVT[b] $N = 2,305$**	**Group C PE ± any DVT $N = 2,451$**	**Total $N = 5,772$**
Age, y; mean ± SD	58.2 ± 17.5 **[57.1–59.3]**	61.8 ± 17.0 **[61.1–62.5]**	63.0 ± 16.5 **[62.4–63.7]**	61.7 ± 17.0 YY
Age group, *n* (%)				
< 65 y	603 (59.4) **[56.3–62.4]**	1182 (51.3) **[49.2–53.3]**	1190 (48.6) **[46.6–50.6]**	2975 (51.5) YY
65 to <75 y	211 (20.8) [18.3–23.4]	542 (23.5) [21.8–25.3]	575 (23.5) [21.8–25.2]	1,328 (23.0)
≥75 y	202 (19.9) **[17.5–22.5]**	581 (25.2) **[23.4–27.0]**	686 (28.0) **[26.2–29.8]**	1,469 (25.5) YY
Male,[c] *n* (%)	496 (48.8) [45.7–51.9]	1,221 (53.0) [50.9–55.0]	1,208 (49.3) [47.3–51.3]	2,925 (50.7)
Ethnicity, *n* (%)				
White	830 (81.7) **[78.2–84.0]**	1,812 (78.6) [76.9–80.3]	1,737 (70.9) **[69.0–72.7]**	4,379 (75.9) Y
Asian	102 (10.0) [8.3–12.1]	202 (8.8) [7.6–10.0]	330 (13.5) [12.1–14.9]	634 (11.0)
Black or African American	11 (1.1) **[0.5–1.9]**	54 (2.3) [1.8–3.0]	104 (4.2) **[3.5–5.1]**	169 (2.9) Y
Unknown	72 (7.1) [5.6–8.8]	228 (9.9) [8.7–11.2]	264 (10.8) [9.6–12.1]	564 (9.9) Y
Other[d]	1 (0.1) [0.00–0.05]	9 (0.4) [0.2–0.7]	16 (0.7) [0.4–1.1]	26 (0.5)
CrCl,[e] mL/min, mean ± SD	102.0 ± 43.0 **[98.5–105.5]**	92.1 ± 42.8 **[89.3–94.3]**	94.2 ± 47.2 **[92.1–96.3]**	94.5 ± 45.1 YY
BMI,[f] kg/m^2, mean ± SD	27.9 ± 5.3 [27.5–28.3]	28.0 ± 5.7 [27.7–28.3]	28.4 ± 6.7 [28.1–28.7]	28.2 ± 6.1
Weight,[g] kg, mean ± SD	80.6 ± 18.3 [79.4–81.8]	80.6 ± 19.3 [80.0–81.5]	81.8 ± 21.9 [80.9–82.7]	81.1 ± 20.3
Height,[h] cm, mean ± SD	169.7 ± 10.0 [168.0–169.4]	169.3 ± 9.9 [168.9–169.8]	169.3 ± 10.5 [168.8–169.8]	169.4 ± 10.2
Prior VTE event, *n* (%)	108 (10.6) [8.8–12.7]	289 (12.5) [11.2–14.0]	235 (9.6) [8.5–10.8]	632 (10.9)

(*Continued*)

Table 2 (*Continued*)

	Group A IDDVT[a] *N* = 1,016	Group B PDVT ± DDVT[b] *N* = 2,305	Group C PE ± any DVT *N* = 2,451	Total *N* = 5,772
Smoking history,[i] *n* (%)				
Non-smoker	501 (49.3) [46.2–52.4]	1,081 (46.9) [44.8–49.0]	1,193 (48.7) [46.7–50.7]	2,775 (48.1)
Current smoker	180 (17.7) **[15.4–20.2]**	369 (16.0) [14.5–17.6]	330 (13.5) **[12.1–14.9]**	886 (15.2) Y
Ex-smoker	103 (10.1) **[8.4–12.2]**	297 (12.9) [11.4–14.3]	411 (16.8) **[15.3–18.3]**	811 (14.1) Y
Unknown	232 (22.8) [20.3–25.5]	558 (24.2) [22.5–26.0]	516 (21.1) [19.5–22.7]	1,306 (22.6)
Insurance status for medication,[j] *n* (%)				
Public insurance	535 (52.7) **[49.5–55.8]**	1,152 (50.0) [47.9–52.0]	1,059 (43.2) **[41.2–45.2]**	2,746 (47.6) Y
Private insurance	41 (4.0) **[2.9–5.4]**	119 (5.2) [4.3–6.1]	164 (6.7) **[5.7–7.8]**	324 (5.6) Y
Out-of-pocket	87 (8.6) **[6.9–10.5]**	206 (8.9) [7.8–10.2]	102 (4.2) **[3.4–5.0]**	395 (6.8) Y
Multiple types	35 (3.4) [2.4–4.8]	110 (4.8) [3.9–5.7]	131 (5.3) [4.5–6.3]	276 (4.8)
Employment status,[k] *n* (%)				
Retired	275 (27.1) **[24.4–29.9]**	833 (36.1) **[34.2–38.1]**	802 (32.7) **[30.9–34.6]**	1,910 (33.1) YY
Works full time	306 (30.1) **[27.3–33.0]**	534 (23.2) **[21.5–24.9]**	509 (20.8) **[19.2–22.4]**	1,349 (23.4) YY
Unemployed	87 (8.6) **[6.9–10.5]**	222 (9.6) [8.5–10.9]	298 (12.2) **[10.9–13.5]**	607 (10.5) Y
Disabled	12 (1.2) **[0.6–2.1]**	122 (5.3) **[4.4–6.3]**	83 (3.4) **[2.7–4.2]**	217 (3.8) YY
Self-employed	27 (2.7) [1.3–3.8]	42 (1.8) [1.3–2.5]	54 (2.2) [1.7–2.9]	123 (2.1)
Works part-time	24 (2.4) [1.5–3.5]	48 (2.1) [1.5–2.8]	38 (1.6) [1.1–2.1]	110 (1.9)
Other	19 (1.9) [1.1–2.9]	59 (2.6) [2.0–3.3]	57 (2.3) [1.8–3.0]	135 (2.3)
Unknown	270 (26.6) [23.9–29.4]	488 (21.2) [19.5–22.9]	634 (25.9) [24.1–27.6]	1,392 (24.1)

Abbreviations: BMI, body mass index; CrCl, creatinine clearance; DDVT, distal DVT; DVT, deep vein thrombosis; IDDVT, isolated DDVT; PDVT, proximal DVT; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism.

Notes: Values in square brackets are 95% confidence intervals. **Bold** font indicates 95% confidence intervals which had no overlap between group A and either group B or group C or both; Y indicates no overlap with one other group; YY indicates no overlap with two other groups.

[a]No iliac vein or proximal lower limb DVT, and no PE.

[b]Iliac vein or proximal lower limb DVT (popliteal vein and above), but no PE.

[c]Missing sex data for one patient in group C.

[d]Includes 18 patients with multiple answers, four who were American Indian or Alaskan Native, and four who were Native Hawaiian or other Pacific Islander.

[e]Missing CrCl data for 436 patients in group A, 801 in group B, and 554 in group C.

[f]Missing BMI data for 213 patients in group A, 488 in group B, and 557 in group C.

[g]Missing weight data for 155 patients in group A, 338 in group B, and 377 in group C.

[h]Missing height data for 210 patients in group A, 482 in group B, and 546 in group C.

[i]Missing smoking status data for one patient in group C.

[j]Missing insurance status data for 318 patients in group A, 718 in group B, and 995 in group C.

[k]Patients could have more than one employment status.

Table 3 Management considerations

	Group A IDDVT[a] $N = 1,016$	Group B PDVT ± DDVT[b] $N = 2,305$	Group C PE ± any DVT $N = 2,451$	Total $N = 5,772$
Initial assessment of VTE in ED,[c] *n* (%)	315 (31.0) **[28.2–33.9]**	993 (43.1) **[41.0–45.1]**	1,491 (60.8) **[58.9–62.8]**	2,799 (48.5) YY
Diagnosis setting,[d] *n* (%)				
Hospital	385 (37.9) **[34.9–41.0]**	979 (42.5) [40.4–44.5]	1,075 (43.9) **[41.9–45.9]**	2,439 (42.3) Y
ED	227 (22.3) **[19.8–25.0]**	685 (29.7) **[27.9–31.6]**	1,112 (45.4) **[43.4–47.4]**	2,024 (35.1) YY
Outpatient care center/clinic	238 (23.4) **[20.9–26.2]**	431 (18.7) **[17.1–20.4]**	208 (8.5) **[7.4–9.7]**	877 (15.2) YY
Private practice office	165 (16.2) **[14.0–18.7]**	206 (8.9) **[7.8–10.2]**	56 (2.3) **[1.7–3.0]**	427 (7.4) YY
Admitted to hospital,[e] *n* (%)	297 (29.2) **[26.4–32.1]**	1,118 (48.5) **[46.4–50.6]**	1,839 (75.0) **[73.3–76.7]**	3,254 (56.4) YY
Treated in specialist care unit,[f] *n* (%)	19 (1.9) **[1.1–2.9]**	82 (3.6) [2.8–4.4]	461 (18.8) **[17.3–20.4]**	562 (9.7) Y

Abbreviations: DDVT, distal DVT; DVT, deep vein thrombosis; ED, emergency department; IDDVT, isolated DDVT; PDVT, proximal DVT; PE, pulmonary embolism; VTE, venous thromboembolism.
Notes: Values in square brackets are 95% confidence intervals. **Bold** font indicates 95% confidence intervals which had no overlap between group A and either group B or group C or both; Y indicates no overlap with one other group; YY indicates no overlap with two other groups.
[a]No iliac vein or proximal lower limb DVT, and no PE.
[b]Iliac vein or proximal lower limb DVT (popliteal vein and above), but no PE.
[c]Data missing for one patient in group A and three in group B.
[d]Data missing for one patient in group A and four in group B.
[e]Data missing for one patient in group A and three in group B.
[f]Data missing for 267 patients in group A, 524 in group B, and 479 in group C.

Clinical Management Considerations

The likelihood of having initial assessment of VTE in an emergency department increased with the seriousness of the index event (31.0% in the IDDVT group vs. 43.1 and 60.8% in the PDVT ± DDVT and PE ± DVT groups, respectively), as did the likelihood of being diagnosed in an emergency department (22.3, 29.7, and 45.4%, respectively), and the likelihood of being admitted to hospital for VTE (29.2, 48.5, and 75.0%, respectively; ►**Table 3**).

►**Table 4** summarizes the DVT symptoms and investigations. Investigators reported leg tenderness/pain in approximately 78% of patients with IDDVT or PDVT ± DDVT, compared with 50% in the PE ± DVT group. Other symptoms were less common in the IDDVT group than in the PDVT ± DDVT group: leg swelling, 74.1 versus 87.5%; skin warmth, 17.6 versus 23.8%; and skin discoloration, 18.0 versus 23.5%, respectively. Venous ultrasonography was used for DVT examination in 90.6% of patients, with 2.2% examined using conventional venography and 6.2% using other methods. For investigation of PE, chest computed tomographic scans were performed in 69.8%, pulmonary angiography in 28.9%, ventilation/perfusion lung scan in 10.0%, and other examination in 16.7% of patients.

VTE Risk Factors and Comorbidities

Selected clinical features (comorbidity and/or medical history) that might be considered as risk factors for VTE are shown in ►**Fig. 1**. Patients with IDDVT had a history of VTE in 10.6% of cases, compared with 12.5% in the PDVT ± DDVT group and 9.6% in the PE ± DVT group. The prevalence of several of the other risk factors was lower in the IDDVT group than in the PDVT ± DDVT and PE ± DVT groups. For example, cancer was reported in 7.5, 10.2, and 12.1% of patients with IDDVT, PDVT ± DDVT, and PE ± DVT, respectively. Approximately 6% of the IDDVT and PDVT ± DDVT groups had trauma or surgery compared with 8% of the PE ± DVT group. An exception to this trend was immobilization, which was reported for 4.0% of the IDDVT group, but 2.8 and 1.9% of patients with PDVT ± DDVT and PE ± DVT, respectively.

►**Figure 2** shows the most frequently reported other comorbidities at the baseline visit. Typically, these were also more prevalent in the patients with PDVT ± DDVT or with PE ± DVT compared with the IDDVT group (e.g., hypertension, diabetes mellitus, coronary artery disease, heart failure, and myocardial infarction). Varicose veins were more common in the IDDVT group (5.1%) than in the PDVT ± DDVT (3.2%) and PE ± DVT (2.1%) groups. Superficial thrombophlebitis and venous insufficiency were also found more frequently in patients with DVT than in the group with PE ± DVT.

Anticoagulant Treatments

More than half of the patients with IDDVT (55.6%), PDVT ± DDVT (54.7%), and PE ± DVT (52.8%) were treated with NOACs (►**Fig. 3**). VKAs were the next most frequently prescribed anticoagulant option.

Table 4 DVT symptoms and investigations

	Group A IDDVT[a]	Group B PDVT ± DDVT[b]	Group C PE ± any DVT	Total
Patients with DVT, *n* (%)	1,016 (100)	2,305 (100)	863 (100)	4,184 (100)
Leg tenderness/pain,[c] *n* (%)	795 (78.2) **[75.6–80.7]**	1,796 (77.9) [76.2–79.6]	428 (49.6) **[46.2–53.0]**	3,019 (72.2) Y
Leg swelling,[d] *n* (%)	753 (74.1) **[71.3–76.8]**	2,016 (87.5) **[86.0–88.8]**	502 (58.2) **[54.8–61.5]**	3,271 (78.2) YY
Skin warmth,[e] *n* (%)	179 (17.6) **[15.3–20.1]**	549 (23.8) **[22.1–25.6]**	115 (13.3) **[11.1–15.8]**	843 (20.1) YY
Skin discoloration,[f] *n* (%)	183 (18.0) **[15.7–20.5]**	542 (23.5) **[21.8–25.3]**	104 (12.1) [11.1–15.8]	829 (19.8) Y
Type of investigation,[g] *n* (%)				
Venous ultrasonography	921 (90.6) [88.7–92.4]	2,102 (91.2) [90.0–92.3]	766 (88.8) [86.5–90.8]	3,789 (90.6)
Conventional venography	22 (2.2) [1.4–3.3]	78 (3.4) [2.7–4.2]	39 (4.5) [3.2–6.1]	139 (3.3)
Other	63 (6.2) [4.8–7.9]	151 (6.6) [5.6–7.6]	45 (5.2) [3.8–6.9]	259 (6.2)

Abbreviations: DDVT, distal DVT; DVT, deep vein thrombosis; IDDVT, isolated DDVT; PDVT, proximal DVT; PE, pulmonary embolism.
Notes: Values in square brackets are 95% confidence intervals. **Bold** font indicates 95% confidence intervals which had no overlap between group A and either group B or group C or both; Y indicates no overlap with one other group; YY indicates no overlap with two other groups.
[a]No iliac vein or proximal lower limb DVT, and no PE.
[b]Iliac vein or proximal lower limb DVT (popliteal vein and above), but no PE.
[c]Data unknown for 28 patients in group A, 81 in group B, and 42 in group C.
[d]Data unknown for 28 patients in group A, 58 in group B, and 29 in group C.
[e]Data unknown for 66 patients in group A, 173 in group B, and 60 in group C.
[f]Data unknown for 71 patients in group A, 160 in group B, and 60 in group C.
[g]Data unknown for 19 patients in group A, 38 in group B, and 51 in group C.

As shown in ►**Table 5**, 19.3% of all patients received parenteral anticoagulation only during the initial treatment period (up to 14 days or hospital discharge, whichever was later). Unfractionated heparin (UFH) was administered slightly more frequently in patients with PE than in DVT alone: IDDVT (0.7%), PDVT ± DDVT (1.2%), and PE ± DVT (2.9%). There was a similar pattern for low-molecular-weight heparin (LMWH) alone. The once-daily regimen was favored over twice daily in the IDDVT group. The percentages of patients who received parenteral therapy prior to oral anticoagulation during the initial treatment period were 48.4% for IDDVT, 53.4% for PDVT ± DDVT, and 59.4% for PE ± DVT. The same distribution between UFH and LMWH, and once and twice daily, respectively, was observed, as for parenteral therapy only.

Discussion

Our findings show that nearly one-fifth of patients with acute VTE presented with IDDVT alone. These patients were younger and had fewer VTE risk factors and other comorbidities than the patients with PDVT ± DDVT or PE ± DVT. There were differences in clinical presentation and management settings among the groups, but only small differences in the choice of anticoagulant therapy.

Several noninterventional studies have provided data on the real-world use of anticoagulants in patients with IDDVT and PDVT. These included a single-center cohort in Italy, and respective cohorts in the international RIETE registry, the French OPTIMEV study, and the global GARFIELD-VTE registry (►**Table 6**).[13–16,18] GARFIELD-VTE also included data on patients with PE ± DVT.[16] We note that the analysis of the single-center cohort excluded patients with prior VTE,[13] whereas the other studies, and RE-COVERY DVT/PE, did not apply this exclusion. For the OPTIMEV study, a separate analysis of the subgroup with a first event has been presented.[19] In our study, the proportion of patients with prior VTE was 10 to 12%. Despite the possibility that prior episodes of VTE may influence the composition of risk factors, comorbidities, and choices of anticoagulants, these patients were not analyzed separately due to their small number.

In all studies, patients with IDDVT were younger than those with PDVT or PE ± DVT. The most similar study in terms of scope and observation dates was GARFIELD-VTE, involving 10,088 patients with VTE from 28 countries worldwide between 2014 and 2017. The GARFIELD-VTE study was consistent with RE-COVERY DVT/PE in finding that approximately one-fifth of patients had IDDVT, 40% had PDVT, and 40% had PE ± DVT. In both studies, IDDVT accounted for approximately 31 to 36% of the patients with DVT (without PE).[16] The proportion with IDDVT was similar in RIETE (17.3%) and the Italian cohort study (24.3%), but was much higher in OPTIMEV (56.8%). Differences may be explained by differences in study settings and, mainly, by differences in ultrasound protocols.[14,15,20] In France, Germany, Austria, and Switzerland,

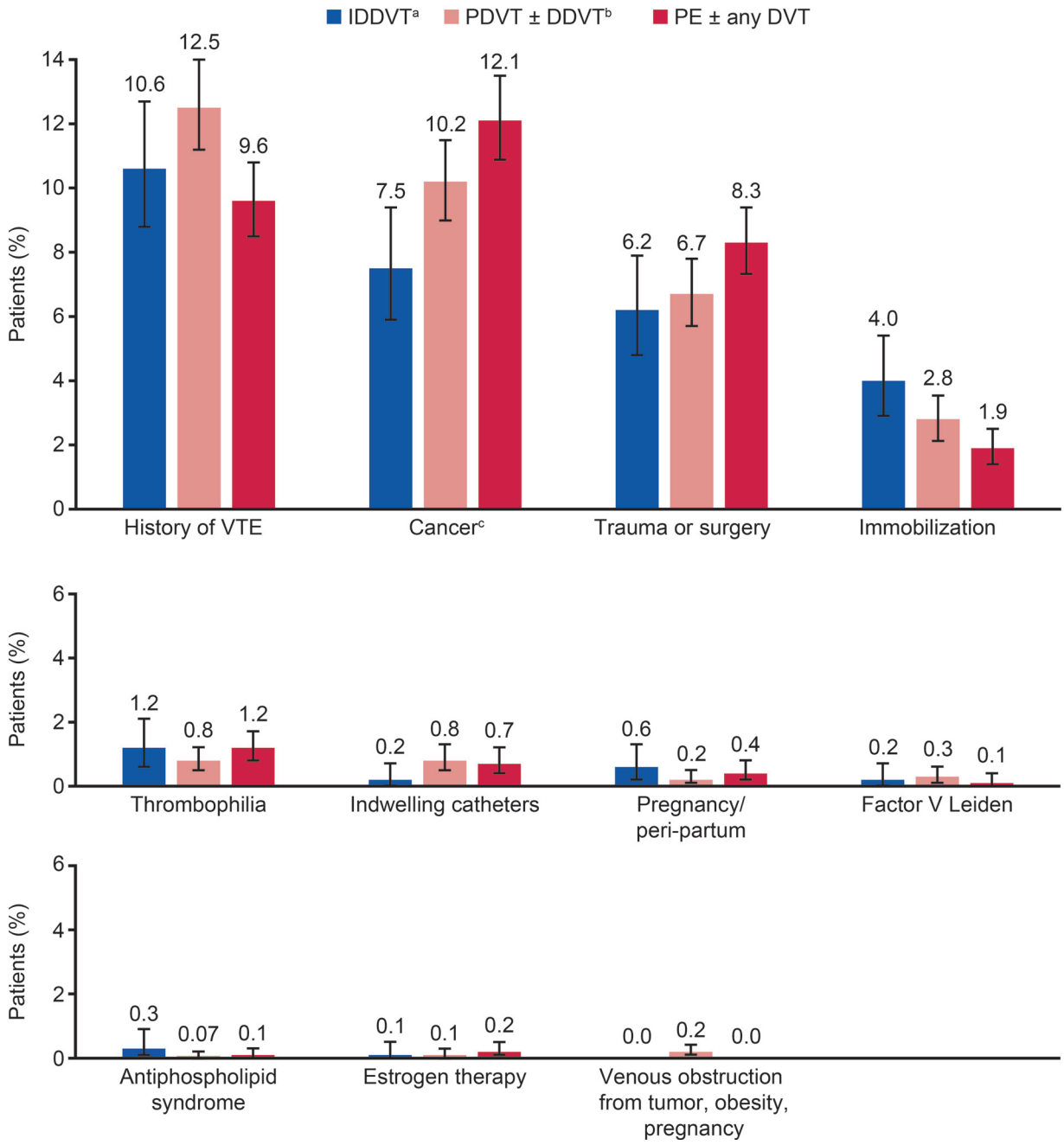

Fig. 1 Risk factors for VTE according to type and location of index VTE. Note: Based on discussion of the literature, the authors selected 11 clinical features as potential risk factors for VTE. The total numbers (%) of patients with any of the selected risk factors were as follows: IDDVT, 268 (28.4); PDVT ± DDVT, 688 (29.8); and PE ± DVT, 729 (29.7). DDVT, distal DVT; DVT, deep vein thrombosis; IDDVT, isolated DDVT; PDVT, proximal DVT; PE, pulmonary embolism; VTE, venous thromboembolism. Error bars show the 95% confidence intervals. [a]No iliac vein or proximal lower limb DVT, and no PE. [b]Iliac vein or proximal lower limb DVT (popliteal vein and above), but no PE. [c]Cancer excluding nonmelanoma skin cancer.

and to a lesser extent in Italy, almost all sonographers examine the calf veins in all patients with suspected DVT. Ultrasound protocols differ substantially across countries and even between sites within the same country. This directly influences the recorded proportion with IDDVT.

While IDDVT was detected in similar proportions of Caucasians and Asians (19 and 16% in RE-COVERY; 21 and 22% in GARFIELD-VTE), fewer Black or African American patients had IDDVT detected (7% in RE-COVERY DVT/PE and 11% in GARFIELD-VTE).[16] This equates to a ratio of IDDVT:PDVT of 0.46 in Caucasians and 0.50 in Asians, but 0.20 in Black or African American patients. GARFIELD-VTE showed similar results: a ratio of 0.59 in Caucasians and 0.55 in Asians, but 0.20 in Black or African American patients. These observations raise the question of detection bias due to underlying health care disparities. There might be a higher threshold to seek medical care among Black or African American patients. Variations in diagnostic testing might be another reason for the country differences observed in GARFIELD-VTE, where the ratio of IDDVT:PDVT ranged from

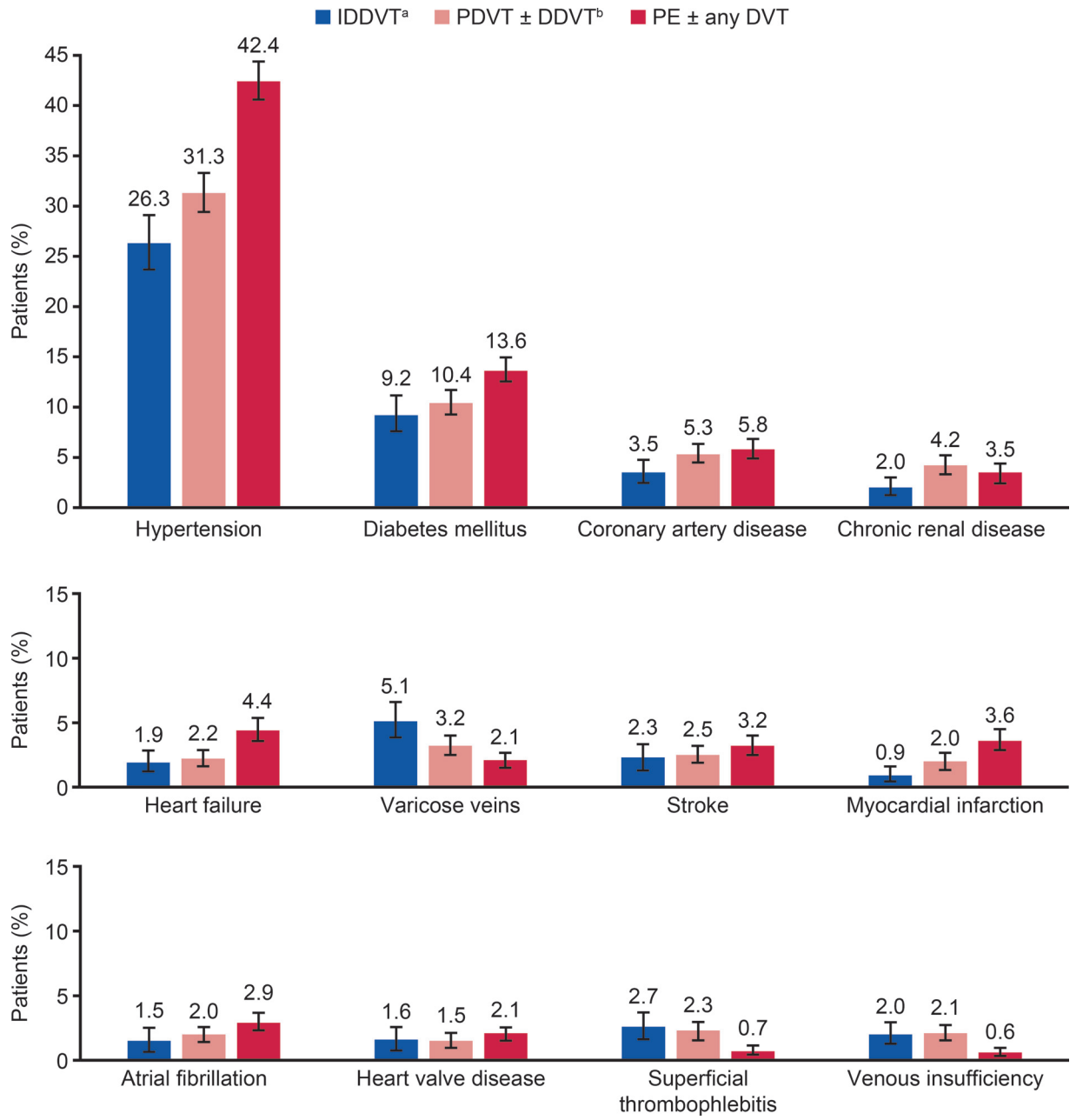

Fig. 2 Other comorbidities and/or medical history according to type and location of index VTE. Note: Other comorbidities and/or medical history include clinical features other than those selected by the authors as potential risk factors for VTE (see ►**Fig. 1**). Comorbidities and/or medical history present in ≥2% of patients in any subgroup. Patients could have more than one comorbidity and/or medical history. The following were considered: atrial fibrillation, Behcet's disease, chemical phlebitis, chronic hepatic disease, chronic renal disease, coronary artery disease, diabetes mellitus, disseminated intravascular coagulation, hemolytic anemias, heart failure, heart valve disease, hypertension, inflammatory bowel disease, myocardial infarction, nephrotic syndrome, peripheral vascular disease, rheumatoid arthritis, sepsis, stroke, superficial vein thrombosis, systemic lupus erythematosus, varicose veins, venous insufficiency, and venous insufficiency or varicose veins. The total numbers (%) of patients with any of the other comorbidities and/or medical history were as follows: IDDVT, 376 (37.0); PDVT ± DDVT, 1,038 (45.0); and PE ± DVT, 1,333 (54.4). DDVT, distal DVT; DVT, deep vein thrombosis; IDDVT, isolated DDVT; PDVT, proximal DVT; PE, pulmonary embolism; VTE, venous thromboembolism. Error bars show the 95% confidence intervals. [a]No iliac vein or proximal lower limb DVT, and no PE. [b]Iliac vein or proximal lower limb DVT (popliteal vein and above), but no PE.

0.15 (95% CI, 0.11–0.18) in Canada to 1.96 (95% CI, 1.51–2.41) in Australia.[16] With such wide disparities in the diagnosis of IDDVT, it is possible that certain centers/countries under- or overdiagnose IDDVT.

In our study, 60% of IDDVT patients were diagnosed in a hospital or hospital-affiliated setting (22% in an emergency department and 38% in another hospital-associated outpatient facility). A smaller proportion (~29%) of our study patients was hospitalized compared with GARFIELD-VTE, in which 61% were treated as inpatients.[16] These findings highlight the heterogeneity of real-world studies. However, in both studies, IDDVT was less often treated in hospital than PDVT ± DDVT or PE ± DVT, reflecting the anticipated lower severity.

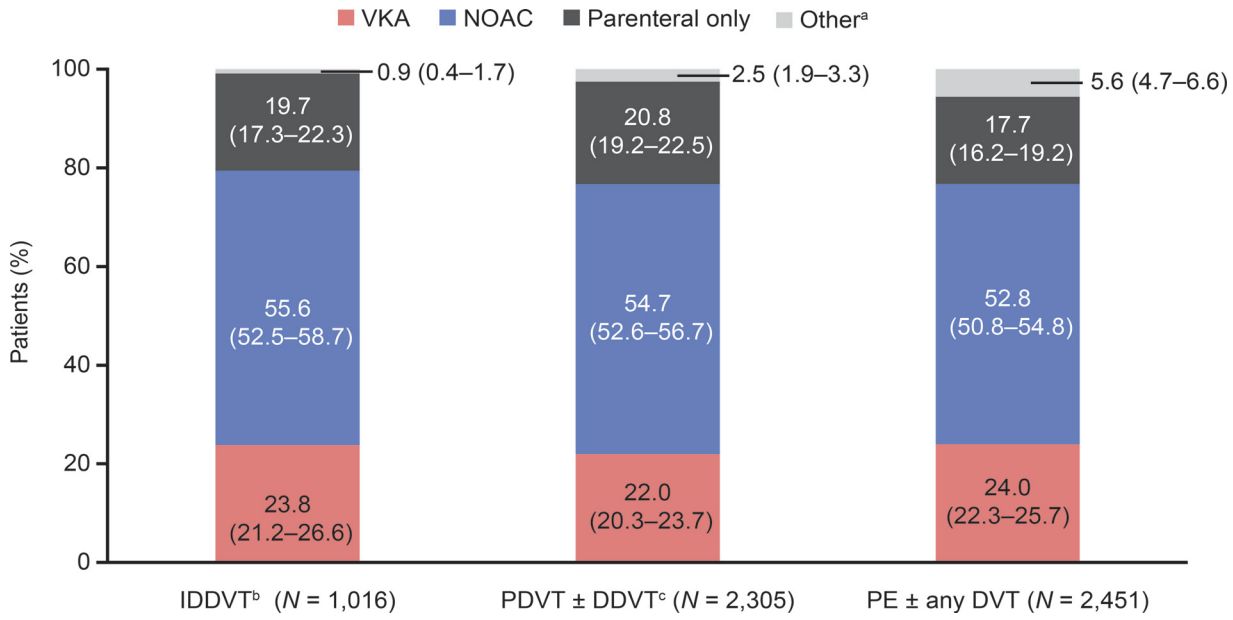

Fig. 3 Main anticoagulation therapy according to type and location of index VTE. DDVT, distal DVT; DVT, deep vein thrombosis; IDDVT, isolated DDVT; PDVT, proximal DVT; NOAC, non-VKA oral anticoagulant; PE, pulmonary embolism; VKA, vitamin K antagonist; VTE, venous thromboembolism. Values in parentheses are 95% confidence intervals. [a]Other includes catheter-directed thrombolysis, systemic thrombolysis, and other treatments, respectively, as follows: 0, 0, and 9 patients in the IDDVT group; 4, 1, and 53 in the PDVT ± DDVT group; and 4, 8, and 125 in the PDVT ± any DVT group. [b]No iliac vein or proximal lower limb DVT, and no PE. [c]Iliac vein or proximal lower limb DVT (popliteal vein and above), but no PE.

Table 5 Details of parenteral anticoagulation therapy given alone or prior to oral anticoagulation in the period from baseline up to hospital discharge or 14 days after diagnosis (whichever was later)

	Group A IDDVT[a] *N* = 1,016	**Group B PDVT ± DDVT[b] *N* = 2,305**	**Group C PE ± any DVT *N* = 2,451**	**Total *N* = 5,772**
Details of parenteral anticoagulation therapy alone				
Parenteral therapy, *n* (%)	200 (19.7) [17.3–22.3]	480 (20.8) [19.2–22.5]	433 (17.7) [16.2–19.2]	1,113 (19.3)
UFH, *n* (%)	7 (0.7) **[0.3–1.4]**	27 (1.2) [0.8–1.7]	71 (2.9) **[2.3–3.6]**	105 (1.8) Y
LMWH, *n* (%)	195 (19.2) [16.8–21.8]	472 (20.5) [18.8–22.2]	416 (17.0) [15.5–18.5]	1,083 (18.8)
Frequency[c]				
QD	131 (67.2) **[60.1–73.7]**	262 (55.5) [50.9–60.1]	184 (44.2) **[39.4–49.2]**	577 (53.3) Y
BID	64 (32.8) **[26.3–39.9]**	206 (43.6) [39.1–48.3]	224 (53.8) **[48.9–58.7]**	494 (45.6) Y
Other or missing	0	4 (0.8) [0.2–2.2]	8 (1.9) [0.8–3.8]	12 (1.1)
Fondaparinux, *n* (%)	4 (0.4) [0.1–1.0]	9 (0.4) [0.2–0.7]	9 (0.4) [0.2–0.7]	22 (0.4)
Details of parenteral anticoagulation therapy prior to oral anticoagulant therapy				
Parenteral therapy, *n* (%)	492 (48.4) [45.3–51.5]	1,230 (53.4) [51.3–55.4]	1,455 (59.4) [57.4–61.3]	3,177 (55.0)
UFH, *n* (%)	58 (5.7) [4.4–7.3]	322 (14.0) [12.6–15.5]	380 (15.5) [14.1–17.0]	760 (13.2)
LMWH, *n* (%)	435 (42.8) [39.7–45.9]	925 (40.1) [38.1–42.2]	1,203 (49.1) [47.1–51.1]	2,563 (44.4)

(*Continued*)

Table 5 (*Continued*)

	Group A IDDVT[a] $N = 1{,}016$	Group B PDVT ± DDVT[b] $N = 2{,}305$	Group C PE ± any DVT $N = 2{,}451$	Total $N = 5{,}772$
Frequency[c]				
QD	215 (49.4) **[44.6–54.2]**	366 (39.6) **[36.4–42.8]**	361 (30.0) **[27.4–32.7]**	942 (36.8) YY
BID	211 (48.5) **[43.7–53.3]**	540 (58.4) **[55.1–61.6]**	809 (67.2) **[64.5–69.9]**	1,560 (60.9) YY
Other or missing	4 (0.9) [0.3–2.3]	9 (1.0) [0.4–1.8]	9 (0.7) [0.3–1.4]	22 (0.4)
Fondaparinux, *n* (%)	8 (0.8) [0.3–1.5]	25 (1.1) [0.7–1.6]	39 (1.6) [1.2–2.3]	72 (1.2)

Abbreviations: BID, twice daily; DDVT, distal DVT; DVT, deep vein thrombosis; IDDVT, isolated DDVT; LMWH, low-molecular-weight heparin; PDVT, proximal DVT; PE, pulmonary embolism; QD, once daily; UFH, unfractionated heparin.
Notes: Values in square brackets are 95% confidence intervals. **Bold** font indicates 95% confidence intervals which had no overlap between group A and either group B or group C or both; Y indicates no overlap with one other group; YY indicates no overlap with two other groups.
[a]No iliac vein or proximal lower limb DVT, and no PE.
[b]Iliac vein or proximal lower limb DVT (popliteal vein and above), but no PE.
[c]Percentages were calculated based on the number of patients who received the respective therapy.

Table 6 Demographics, risk factors, and anticoagulation for IDDVT, PDVT ± DDVT, and PE ± any DVT, reported in observational VTE studies

	Barco et al[13] Single-center, retrospective $N = 831$ Italy, 2000–2012		RIETE,[14] $N = 11{,}086$ 24 countries worldwide 2001–2008		OPTIMEV,[15] $N = 1{,}643$ France, 2004–2006		GARFIELD-VTE,[16] $N = 10{,}088$ 28 countries worldwide 2014–2017			RE-COVERY DVT/PE, $N = 5{,}722$ 34 countries worldwide 2016–2017		
	IDDVT	PDVT	IDDVT	PDVT	IDDVT	PDVT	IDDVT	PDVT	PE	IDDVT	PDVT	PE
Patients, *n* (%)	202 (24.3)	629 (75.7)	1,921 (17.3)	9,165 (82.7)	933 (56.8)	710 (43.2)	2,145 (21.3)	3,846 (38.1)	4,097 (40.6)	1,016 (17.6)	2,305 (39.9)	2,415 (42.5)
Female, %	56	49	49	48	58	52	52	49	49	51	47	51
Age, mean or median, years	66	67	65	70	62	69	56	58	60	58	62	63
Caucasian ethnicity, %	–	–	–	–	–	–	69.1	64.1	73.6	81.7	78.6	70.9
Risk factors, %												
History of VTE	3[a]	5[a]	15	17	29	34	14	17	15	11	13	10
Active cancer	24	23	14	22	11	20	7	10	10	8	10	12
Trauma/surgery	14/21	9/17	–/15	–/11	–/22	–/12	13/15	9/11	5/13	6 (either)	7 (either)	8 (either)
Immobilization	23	17	24	28	18	20	–	–	–	4	3	2
Anticoagulation therapy, %												
Any anticoagulant	97	88	97[b]	97[b]	81[c]	92[c]	97[d]	98[d]	98[d]	–	–	–
OAC	32	73	–	–	–	–	–	–	–	–	–	–
VKA	–	–	–	–	70[c]	70[c]	24[d]	31[d]	30[d]	24[e]	22[e]	24[e]
NOAC	–	–	–	–	–	–	50[d]	46[d]	47[d]	56[e]	55[e]	53[e]
Parenteral only	–	–	–	–	–	–	17[d]	16[d]	16[d]	20[e]	21[e]	18[e]

Abbreviations: DDVT, distal DVT; DVT, deep vein thrombosis; GARFIELD-VTE: The Global Anticoagulant Registry in the FIELD-Venous Thromboembolic Events; IDDVT, isolated DDVT; NOAC, non-VKA oral anticoagulant; OAC, oral anticoagulant; OPTIMEV: OPTimisation de l'Interrogatoire dans l'évaluation du risque throMbo-Embolique Veineux; PDVT, proximal DVT; PE, pulmonary embolism; RIETE: Registro Informatizado de pacientes con Enfermedad TromboEmbólica; VKA, vitamin K antagonist; VTE, venous thromboembolism.
[a]Family history of VTE.
[b]For ≥10 days.
[c]For 3-month follow-up period.
[d]For ≤30 days.
[e]Up to hospital discharge or 14 days after diagnosis (whichever was later).

IDDVT is associated with transient risk factors such as hospitalization and pregnancy/postpartum, while PDVT is associated more with chronic risk factors and systemic disease such as history of VTE and active cancer.[21] Differing risk factor profiles for IDDVT and PDVT are presented in ►**Table 6**. Similar to our data, RIETE, OPTIMEV, and GARFIELD-VTE all showed that lower proportions of patients with IDDVT had active cancer or a history of VTE compared with the PDVT group.[14–16]

Similar to RE-COVERY DVT/PE, there were relatively small differences in the choice of anticoagulant for IDDVT versus PDVT in GARFIELD-VTE.[16,22] However, Barco et al reported that 32 and 65% of patients with IDDVT received either oral anticoagulants or LMWH/fondaparinux, respectively, compared with 73 and 25% of those with PDVT.[13] The use of LMWH or fondaparinux presumably reflects a shorter-term anticoagulation strategy for patients with IDDVT, as median duration of anticoagulation was 70 days in the IDDVT group compared with 238 days in the PDVT group.[13] Notably, our results from RE-COVERY DVT/PE showed that 99.3% of enrolled patients received anticoagulant therapy. Similarly, in other real-world studies, most IDDVT patients were treated with anticoagulant therapy (►**Table 6**).[13,14,16,18] This finding demonstrates that, in the real-world setting, the selection of anticoagulant therapy as the initial treatment for IDDVT is not different from that for PDVT ± DDVT. In particular, the strategy of no treatment, albeit mentioned in guidelines and investigated in randomized clinical trials, is rare. Given the limited evidence from randomized controlled trials for a net benefit of anticoagulation in patients with IDDVT, and given the low propagation rate of IDDVT of up to 10 to 20%, these findings may point to a global, significant anticoagulant overuse in a majority of IDDVT patients. Our data provide a basis for future prospective studies investigating risk factors for IDDVT propagation necessitating anticoagulation, or—vice versa—low risk markers, justifying a wait-and-watch strategy in these patients.

We note potential limitations of the study. All diagnostic and treatment information was reported by the investigators with no central or external review, and not all patients would have been examined with both leg vein imaging and computed tomography pulmonary angiography or a ventilation/perfusion scan. Thus, the distribution of sites of VTE that we have reported should be interpreted with caution and may not represent the natural history of VTE. By contrast, the study provides a global perspective of how physicians diagnose and treat patients with IDDVT.

Conclusion

These data from the RE-COVERY DVT/PE study demonstrate that, although differences in patient characteristics, risk factors, and clinical management were identified, the selection of initial anticoagulant therapy for IDDVT is not different from that for PDVT ± DDVT. Prospective studies should investigate whether, in a global perspective, this is an appropriate use of anticoagulants.

Note

Trial registration number (ClinicalTrials.gov) is NCT025 96230.

Authors' Contributions

S.S. was responsible for the concept of the secondary analyses presented in this manuscript. W.T. was responsible for the data analysis. All authors were responsible for the study concept and design; interpretation of the data; preparation, review, or approval of the manuscript; revision of intellectual content; and the decision to submit the manuscript for publication.

Conflict of Interest

S. Schellong has received speaker fees from Bayer HealthCare, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, GlaxoSmithKline, Sanofi, and LEO Pharma. He has received consultancy fees from Bayer HealthCare, Boehringer Ingelheim, Daiichi Sankyo, GlaxoSmithKline, and Sanofi. W. A. has participated in advisory boards for Bayer, Portola, Aspen, Sanofi, Daiichi Sankyo, and Boehringer Ingelheim, and has received travel or research support from Bayer, Portola, Aspen, Janssen, Sanofi, Daiichi Sankyo, Bristol-Myers Squibb, Pfizer, and Boehringer Ingelheim. I.B.C. has received speaker and/or consultancy fees from Boehringer Ingelheim, Bayer, Daiichi Sankyo, Pfizer, and Amgen. K.H.C. has received speaker fees from Boehringer Ingelheim, Bristol-Myers Squibb, and Pfizer. S. Schulman has received honoraria from Boehringer Ingelheim, Bayer HealthCare, Daiichi Sankyo, and Sanofi, and research support from Boehringer Ingelheim, Baxter, and Octapharma. D.E.S. has received honoraria from Boehringer Ingelheim, Bristol-Myers Squibb, Merck, Johnson & Johnson, and Pfizer, and research support from Boehringer Ingelheim and Bristol-Myers Squibb. M. D., W.T., I.V., and K.Z. are employees of Boehringer Ingelheim. S.Z.G. has received research support from Boehringer Ingelheim, Bristol-Myers Squibb, BTG EKOS, Daiichi Sankyo, Janssen, the US National Heart Lung and Blood Institute, and the Thrombosis Research Institute. He is a consultant for Bayer and Boehringer Ingelheim.

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