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ORIGINAL ARTICLE

The venous thrombosis registry in Østfold Hospital (TROLL registry) - design and cohort description

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Abstract

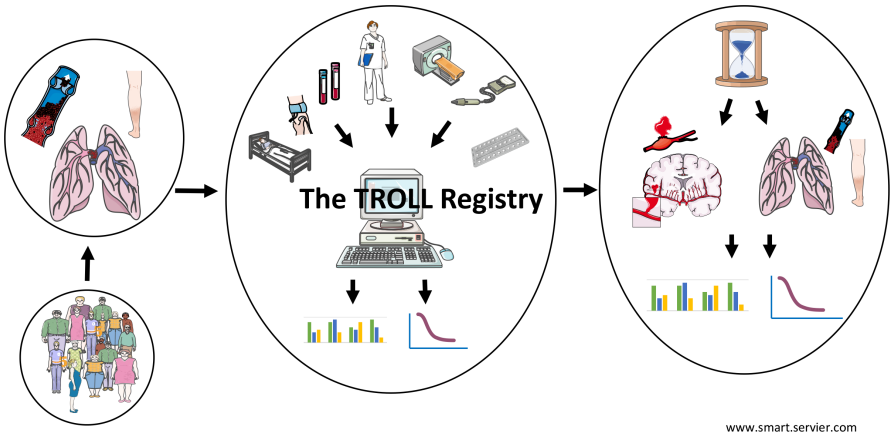
Purpose: The incidence of venous thromboembolism (VTE) is expected to increase over the next decades, further increasing its substantial impact on patients and health care resources. Registries have the benefit of reporting real-world data without excluding clinically important subgroups. Our aim was to describe a Norwegian VTE registry and to provide descriptive data on the population and management.

Registry Population: The Venous Thrombosis Registry in Østfold Hospital (TROLL) is an ongoing registry of consecutive patients diagnosed with, treated, and/or followed up for VTE at Østfold Hospital, Norway, since 2005. Baseline and follow-up data, including demographics, clinical features, risk factors, diagnostic procedures, classification of VTE, and treatment were collected during hospitalization, and at scheduled outpatient visits.

Findings to Date: From January 2005 to June 2021, 5037 patients were eligible for research in TROLL. Median age was 67 years (interquartile range, 55–77), and 2622 (52.1%) were male. Of these, 2736 (54.3%) had pulmonary embolism (PE), 2034 (40.4%) had deep vein thrombosis (DVT), and 265 (5.3%) had upper-extremity DVT or splanchnic or cerebral sinus vein thrombosis. In total, 2330 (46.3%) were classified as unprovoked VTE, and 1131 (22.5%) had cancer. Direct oral anticoagulants were the most frequent therapeutic agents (39.3%) followed by low-molecular-weight heparins (30.4%) and vitamin K antagonists (30.3%). Outpatient treatment for PE increased from 4% in 2005 to 23% in 2019.

Future Plans: TROLL is a population-based ongoing registry that represents a valuable source of real-world data that will be used for future research on the management and outcomes of VTE.

KEYWORDS
anticoagulants, cohort, deep vein thrombosis, pulmonary embolism, registry, risk factors, splanchnic thrombosis, venous thromboembolism



Graphical Abstract

Design of the TROLL registry.

Essentials

- The Venous Thrombosis Registry in Østfold Hospital (TROLL) registry comprises more than 5000 unselected patients with venous thromboembolism (VTE).
- TROLL was initiated in 2005, and inclusion is continuously ongoing.
- Baseline characteristics of TROLL correspond well with those of other unselected VTE populations.
- TROLL has a high proportion of patients treated with direct oral anticoagulants.

1 | INTRODUCTION

Venous thromboembolism (VTE) comprises deep vein thrombosis (DVT) of the lower and upper extremities, pulmonary embolism (PE), and thrombosis in rare sites, such as the splanchnic veins or cerebral sinus veins. VTE is considered the third most common cardiovascular disease following myocardial infarction and stroke.[1] According to a recent report,[2] the overall annual incidence rate of VTE in Norway is 1.38 per 1000 person-years (DVT 0.71 per 1000 person-years and PE 0.67 per 1000 person-years). The incidence of VTE has been increasing over the past decades.[3,4] This observation might be due to an increased prevalence of VTE risk factors such as old age, obesity, and cancer, as well as due to improved and more liberal use of diagnostic imaging.[3–5]

According to current guidelines, all patients with VTE should receive anticoagulation therapy for at least 3–6 months.[6] Extended anticoagulation therapy may be warranted to prevent recurrent VTE in high-risk patients,[6] but this comes at the cost of increased bleeding risk. Other short- and long-term complications of VTE include the postthrombotic syndrome, persistent dyspnea, and chronic thromboembolic pulmonary hypertension, which may all impact physical function and health-related quality of life.[7,8] The increasing VTE incidence combined with the potentially severe complications of the disease impose a substantial socioeconomic burden on society and health care systems.[1]

There has been substantial development in the management of VTE over the past 2 decades, exemplified by the introduction of new therapies, optimization of the duration of anticoagulation therapy, and increasing awareness of long-term outcomes. Randomized clinical trials are often limited by extensive exclusion criteria that may lead to underrepresentation of certain high-risk populations, such as elderly or pregnant patients, and those at high risk of bleeding.[9] Therefore, registry-based studies have an important role to document real-world management of these patients and how it may deviate from the controlled setting of a clinical trial. Additionally, they may serve to identify risk factors and prognostic markers for short- and long-term outcomes.

The aim of this paper is to describe the venous Thrombosis Registry in Østfold Hospital (TROLL), including design and methodology, and to provide descriptive data on the populations' demography, risk factors, type of VTE, and treatment patterns.

2 | DESIGN

The TROLL registry is an ongoing, single-center registry of consecutive patients with VTE who are diagnosed, treated, and/or followed up at Østfold Hospital, Norway. Østfold Hospital is the primary referral center and only somatic hospital in Østfold County, and covers a population of 317,000 inhabitants. The TROLL registry was established in 2005. The overall objectives of this study were to describe TROLL registry with regard to the methodology and to provide descriptive data on the populations' demography, risk factors, type of VTE, and treatment patterns.

2.1 | Study population

Consecutive patients aged ≥18 years with objectively verified VTE including PE, DVT (upper and lower extremity), splanchnic vein thrombosis (i.e., thrombosis involving the mesenteric, portal, ovarian, or splenic veins), and cerebral sinus vein thrombosis were included in the registry. To be included in TROLL, the following criteria had to be fulfilled: symptomatic or incidental VTE objectively verified by computed tomography pulmonary angiography (CTPA), compression ultrasonography (CUS), venography, ventilation/perfusion scintigraphy, magnetic resonance imaging, or autopsy. Inclusion took place either at the thrombosis outpatient clinic or in the hospital wards by the thrombosis nurse/physician. According to local practice, all patients with a VTE diagnosis should be referred to the thrombosis clinic for an outpatient follow-up visit. However, a proportion of patients were not referred to the thrombosis clinic, such as those who died during hospitalization or those who were not able to come to the thrombosis clinic. To identify these patients, we additionally searched the hospital discharge registry using the International Classification of Diseases, Tenth Revision (ICD-10) VTE-related codes (I26, I63.6, I80, I81, I82, O22.3, O22.5, O87.1, and O87.3), and data were collected by review of the patients' medical records. For patients included at the thrombosis clinic, informed written consent was obtained at the clinical visit. For patients identified from the hospital discharge registry, informed consent forms were posted to the patients except for those who were deceased. In total, 20% of the participants were not referred to the outpatient clinic. However, over the years the proportion of patients referred to the thrombosis clinic steadily increased, and in 2020 only 10% of the patient were identified via ICD codes. The majority of these were patients not able to come to the follow-up visit or died shortly after being diagnosed with VTE. For these patients, data were collected from medical records.

In 2017, a biobank was established to support the registry. From this time forth, included patients were asked for consent to provide blood and urine samples to the biobank.

2.2 | Data collection

Data were collected by the treating nurse and/or physician during the visit at the thrombosis clinic. Additional information was obtained and recorded through an extensive review of the patient's medical records. For those identified through the hospital discharge registry who did not attend the thrombosis clinic, data were collected solely by review of medical records. Baseline data including demographics, clinical features, diagnostic procedures, classification of VTE, risk factors preceding the event, treatment, and follow-up data were recorded. An overview of the variables and their definitions are outlined in Table 1.

2.3 | Definitions

Patients diagnosed with PE with or without DVT were categorized as having PE, since leg imaging was not performed routinely in patients with PE. Provoked VTE was defined when the patient had one or more of the following risk factors: active cancer 6 months before and 3 months after the VTE, pregnancy/postpartum, use of oral contraceptives, surgery, trauma, immobilization (bed rest for 3 days or more) or long-haul flights (more than 4 h) within the last 12 weeks preceding the VTE diagnosis. The VTE was classified as unprovoked when the patient had no provoking factor. Information on the patient's body height and weight was collected by self-report or measurement at the clinical visit (or alternatively the medical records), and body mass index (BMI) was calculated in kilograms per square meter. According to our local and national guidelines, testing for thrombophilia (protein C, protein S, or antithrombin deficiencies; factor V Leiden; prothrombin or antiphospholipid syndrome) is recommended in patients with unprovoked VTE less than 40 years old, patients with recurrent VTE, and patients with VTE in rare localizations. Anticoagulant treatment was also assessed. Treatment with low-molecular-weight heparin (LMWH) + warfarin was classified as vitamin K antagonist (VKA). Since many patients were treated with LMWH during hospitalization and switched to a direct oral anticoagulant (DOAC) at discharge, a 30-day limit for LMWH use before switching to DOAC was set to categorize the treatment as DOAC (i.e., if the switching to DOAC occurred less than 30 days after LMWH start-up, the treatment was classified as DOAC treatment, while LMWH treatment for more than 30 days was classified as LMWH).

2.4 | Missing data

Data retrieved from clinical visits and medical records relies on thorough assessment and registration by the treating health care professionals. For most patients in TROLL, data were assessed and registered at the thrombosis clinic. However, if data were missing on any items after the clinical visit, these items were cross checked against the patient's medical record and updated if the information was available there. For variables like BMI and "VTE in first-degree relatives," we performed complete case analyses and listed the proportion with missing values.

2.5 | Follow-up

The initial follow-up procedure at the thrombosis clinic involves a standardized schedule for follow-up visits as follows: within 3 weeks from diagnosis; at 3, 6, and 12 months; and hereafter annually. The annual follow-up visits at the outpatient clinic continues as long as the patient is on anticoagulation. Outcomes such as bleeding events and VTE recurrence are registered during long-term follow-up, and the entire registry population is regularly reviewed to ensure completeness of the outcome data, in particular data concerning bleeding, recurrence, and cancer. Currently, there is an ongoing review process to adjudicate all outcomes up to 2020. This review is performed by dedicated study personnel. Recurrent VTEs are identified and recorded in the same way as described above for the initial VTE event and follows the same scheduled visits. Bleeding events

TABLE 1 Overview of variables and definitions in the TROLL registry

	Variables and definitions	
Demography	Age	
	Sex	
	Body mass index	
Clinical features	Symptoms • PE: dyspnea, pain, syncope, hemoptysis, coughing, antibiotics for respiratory symptoms past 4 weeks, fever, asymptomatic • DVT: swelling, pain, redness/hyperpigmentation, venous ectasia	
	Duration of symptoms (from 2019)	
	Vital parameters: blood pressure, heart rate, respiratory rate, oxygen saturation, and body temperature	
	PESI score	
Diagnostic procedures	Laboratory: D-dimer, CRP, TNI/TNT, and BNP/NT-proBNP	
	Type of diagnostic imaging modality: CUS, CTPA, ventilation/perfusion scintigraphy, venography, MRI	
	Echocardiography	
Type of VTE	PE	
	DVT	
	UEDVT	
	Splanchnic venous thrombosis (thrombosis involving the mesenteric, portal, ovarian, or splenic veins)	
	Cerebral sinus vein thrombosis	
	Categorization PE: subsegmental, segmental, lobar, main pulmonary artery DVT: distal (axial and muscle vein), popliteal, proximal, pelvis, vena cava	
Risk factors	Provoked	Active cancer past 6 months (ICD-10 code[s])
		Surgery past 12 weeks (procedure code[s])
		Trauma past 12 weeks (ICD-10 code[s])
		Immobilization past 12 weeks
		Oral contraceptives
		Hormone replacement therapy
		Pregnancy or puerperium
		Long-haul flights >4 h past 12 weeks
	Unprovoked	Previous VTE
		Known thrombophilia • Factor V Leiden (homozygous and heterozygous) • Prothrombin G20210A • Protein C or S or antithrombin deficiencies • Antiphospholipid syndrome
		VTE in first-degree relatives
		Neurological disease with lower-extremity paresis
		No risk factors
Treatment	Type of anticoagulation	
	Duration of anticoagulation	
Outcomes	Bleeding	
	Classified according to the criteria of the Control of Anticoagulation Subcommittee of the ISTH	
	Recurrence Defined as new symptoms of VTE followed by a radiological confirmation and/or physician examination that confirms/suspect and restart anticoagulation therapy	
	Occult cancer When screening is started within 3 months after VTE diagnosis; ICD-10 code is recorded	

Abbreviations: BNP/NT-proBNP, B-type natriuretic protein/N-terminal pro B-type natriuretic protein; CRP, C-reactive protein; CTPA, computed tomography pulmonary angiography; CUS, compression ultrasonography; DVT, deep vein thrombosis; ICD-10, International Classification of Diseases, Tenth Revision; MRI, magnetic resonance imaging; PE, pulmonary embolism; PESI, pulmonary embolism severity index score; TNI/TNT, Troponin I/Troponin T; UEDVT, upper-extremity DVT; VTE, venous thromboembolism.

occurring during anticoagulation is classified according to the criteria established by the Control of Anticoagulation Subcommittee of the ISTH.[10,11]

2.6 | Electronic platform

For data entry, the registry uses the electronic platform software Medinsight, a tool for creating customized medical records, developed at Oslo University Hospital, Norway (www.medinsight.no). The software enables linkage to national and international health registries, facilitating data exchange. The registry is linked to the National Population Registry through an 11-digit identification number that is unique for every citizen in Norway, which ensures continuously updated data on death and migration.

2.7 | Ethics and approvals

The registry follows the European data privacy and security law, General Data Protection Regulation Article 6 No. 1 Letter e, and Article 9 No. 2 Letter j. However, all patients are asked to sign a written informed consent to allow usage of data for research purposes. Patients who do not consent are registered, but their data are solely used for quality control purposes, and they are not included in this report. The publication of the data presented in this report was approved by the Regional Committee for Medical and Health Research Ethics, Reference Number 267223, which allowed for the use of data from those who had consented or were deceased. Patients who withdraw their consent will have their data deleted.

2.8 | Statistical analyses

Descriptive statistics were used to display baseline characteristics of the cohort. Frequencies and percentages were reported for categorical variables, whereas medians and interquartile ranges (IQRs) were reported for continuous variables. Statistical analyses were carried out using Stata version 16.0 (Stata Corporation).

3 | FINDINGS TO DATE

By June 2021, 5623 patients with at least one VTE event were registered in TROLL. Of these, 586 (10%) were excluded due to lack of consent. Hence, a total of 5037 patients from January 2005 to June 2021 were included in the description of the registry population. The median age was 67 years (IQR, 55–77), and 2622 (52.1%) were men. Median BMI was 26.8 (IQR, 23.9–30.4). Demographic characteristics of the cohort are summarized in Table 2. Currently, for the period 2005–2020, the mean follow-up time in the registry was 4.2 years (maximum follow-up, 15.3 years).

3.1 | Risk factors

Table 2 displays risk factors for VTE overall and stratified according to the localization of the VTE. Cancer was the most prevalent risk factor occurring in 1131 (22.5%) of the patients. Of these, 176 patients were diagnosed with cancer within 3 months after the diagnosis of VTE (Table 2). The most common transient risk factor was surgery (17.1%), followed by immobilization (9.7%), while other transient risk factors (trauma, oral contraceptives, hormone replacement therapy, pregnancy/puerperium, and long-haul flights) were less common. In total, 2330 (46.3%) were classified as unprovoked VTE. The highest proportion of unprovoked VTE was observed in the PE group (49%).

3.2 | Clinical manifestations and diagnosis

Pulmonary embolism was the most prevalent VTE diagnosis (54.3%), followed by DVT (40.4%) (Figure 1). Among the DVTs, 631 (31%) were distal and 1403 (69%) were proximal. Between 2005 and 2012, the proportion of patients with VTE with PE diagnosis increased from 46% to 57% (Figure 2). Table 3 describes the clinical manifestations and symptoms at presentation in patients diagnosed with PE and DVT. Dyspnea and pain were the most frequently reported symptoms in patients with PE and occurred in 65.5% and 44.0% of the patients, respectively. Eleven percent had been prescribed antibiotics for respiratory symptoms within 4 weeks prior to their PE diagnosis. Nine percent of patients with PE were incidental, and the majority of these (72%) had known active cancer. In patients with DVT, 87% reported pain, and 82% reported swelling of the affected extremity.

CUS was the most frequently used diagnostic modality for DVT (95.8%), whereas CTPA was the main diagnostic modality for PE (96.8%).

3.3 | Anticoagulant treatment

Overall, DOACs were used in 39.3% of the patients, followed by LMWH 30.4% and VKA 30.3% (Table 4). A total of 92 patients (1.8%) were initially treated with thrombolysis. DOACs were introduced in Norway and used at Østfold Hospital from 2013.[12] The proportion of patients prescribed DOACs increased from 2% in 2012 to 73% in 2020, whereas VKA therapy decreased from 60% in 2012 to 3% in 2020 (Figure 3).

3.4 | In- and outpatient treatment

Overall outpatient treatment increased from 41% in 2005 to 47% in 2019 (Figure 4). Outpatient treatment of DVT increased from 71% in 2005 to 77% in 2019. Outpatient treatment for PE increased from 4% in 2005 to 23% in 2019.

TABLE 2 Demography and risk factors

	Total *n* = 5037	PE *n* = 2736	DVT *n* = 2034	UEDVT *n* = 123	Other *n* = 144
Female, *n* (%)	2415 (47.9)	1351 (49.4)	927 (45.6)	58 (47.2)	79 (54.9)
Male, *n* (%)	2622 (52.1)	1385 (50.6)	1107 (54.4)	65 (52.8)	65 (45.1)
Age, median (IQR)	67 (55–77)	70 (59–78)	64 (52–76)	59 (44–69)	61.5 (46.5–70)
BMI, median (IQR)[a]	26.8 (23.9–30.4)	26.8 (23.8–30.4)	27 (24.2–30.4)	25.7 (22.6–30.2)	27.15 (23.4–30.85)
Cancer, *n* (%)	1131 (22.5)	708 (25.9)	339 (16.7)	34 (27.6)	50 (34.7)
Surgery, *n* (%)	862 (17.1)	409 (14.9)	396 (19.5)	22 (19.9)	35 (24.3)
Trauma, *n* (%)	387 (5.7)	140 (5.1)	239 (11.8)	6 (4.9)	2 (1.4)
Immobilization, *n* (%)	489 (9.7)	256 (9.4)	201 (9.9)	15 (12.2)	17 (11.8)
Oral contraceptives, *n* (%)	104 (2.1)	49 (1.8)	47 (2.3)	5 (4.1)	3 (2.1)
Hormone replacement therapy, *n* (%)	93 (1.8)	41 (1.5)	48 (2.4)	1 (0.8)	3 (2.1)
Pregnancy or puerperium, *n* (%)	50 (1.0)	15 (0.2)	32 (1.6)	2 (1.6)	1 (0.7)
Long-haul flights, *n* (%)	303 (6.0)	157 (5.7)	140 (6.9)	3 (2.4)	3 (2.1)
Previous VTE, *n* (%)	225 (4.5)	114 (4.2)	105 (5.2)	2 (1.6)	4 (2.8)
Known thrombophilia, *n* (%)	126 (2.5)	39 (1.4)	76 (3.7)	0 (0)	11 (7.6)
VTE in first-degree relatives, *n* (%)[a]	479 (12.2)	201 (10.0)	263 (15.5)	2 (2.2)	13 (10.2)
Neurological disease with lower-extremity paresis, *n* (%)	65 (1.3)	28 (1.0)	35 (1.7)	2 (1.6)	0 (0)
Unprovoked, *n* (%)	2330 (46.3)	1340 (49.0)	883 (43.4)	54 (43.9)	53 (36.8)

Note: Category "Other" comprises splanchnic (129) and cerebral sinus vein thrombosis (13). Long-haul flights are defined as flights over 4 h. Known thrombophilia comprises factor V Leiden, prothrombin G20210A, protein C or S or antithrombin deficiencies, and antiphospholipid syndrome.

Abbreviations: BMI, body mass index; DVT, deep vein thrombosis; IQR, interquartile range; PE, pulmonary embolism; UEDVT, upper-extremity DVT.

[a]Missing values: BMI, 1695 (33.7%); VTE in first-degree relatives, 1107 (22.0%).

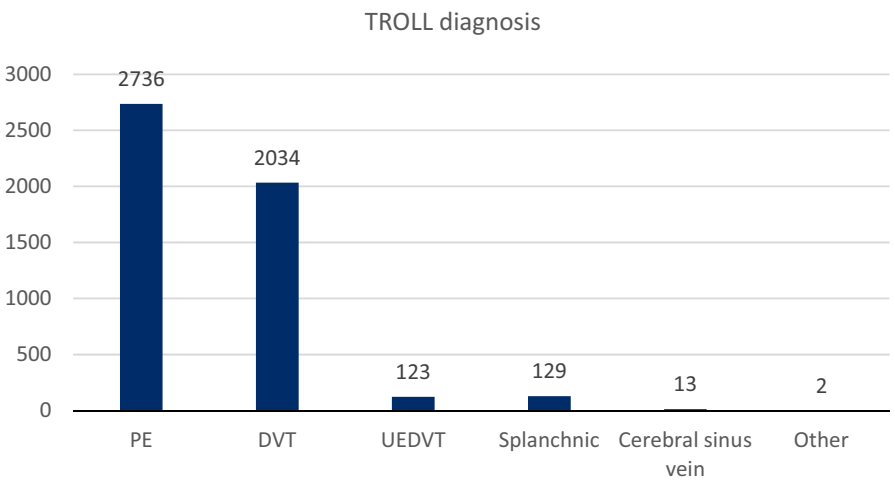


FIGURE 1 Distribution of venous thromboembolism diagnoses in the TROLL registry. Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; UEDVT, upper extremity DVT

4 | DISCUSSION

The TROLL registry is an ongoing dynamic, population-based registry of patients with objectively verified VTE who have been followed up for several years. The registry provides high-quality data on clinical features, management of VTE, and short- and long-term outcomes of various types of VTE. The data in TROLL reflect everyday clinical practice in an unselected patient population and thereby represent a valuable source of real-world data on diagnosis, treatment, and prognosis of VTE. The wide approach for identification and enrollment of patients (i.e., search in the diagnosis registry in addition to the thrombosis clinic visits) ensures that the registry also covers patients who died shortly after the VTE or for other reasons were not able to visit the clinic. Furthermore, the high inclusion rate in TROLL (more than

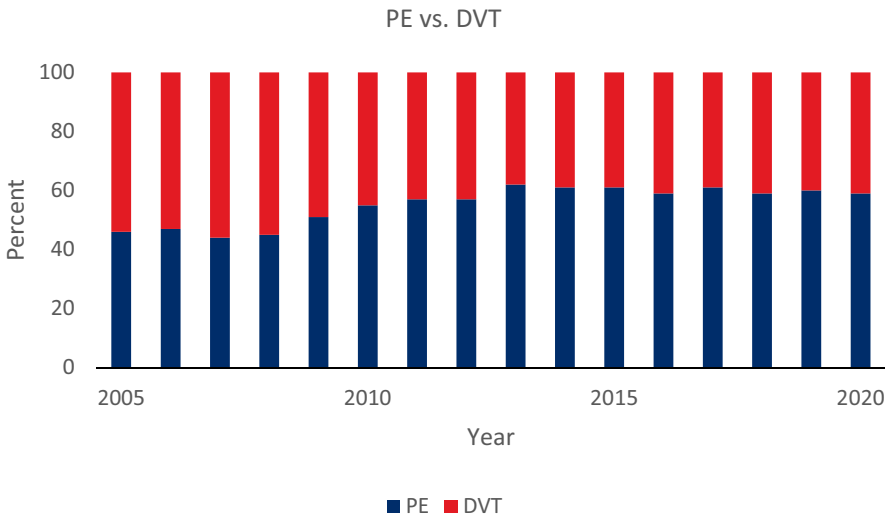


FIGURE 2 Annual proportion of pulmonary embolism (PE) and deep vein thrombosis (DVT) diagnoses during the years 2005–2020

TABLE 3 Distribution of symptoms among patients with PE and DVT

	n (%)
Symptoms PE (*n* = 2460)	
Dyspnea	1798 (73.1)
Pain	1208 (49.1)
Syncope	147 (6.0)
Hemoptysis	47 (1.9)
Coughing	428 (17.4)
Antibiotics for respiratory symptoms past 4 weeks	306 (12.4)
Fever	222 (9.0)
Asymptomatic	249 (10.1)
Symptoms DVT (*n* = 1909)	
Swelling	1786 (93.6)
Pain	1781 (93.3)
Redness, hyperpigmentation	326 (17.1)
Venous ectasia	38 (2.0)

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.

90% of all eligible patients) increases the likelihood of a study sample representative of all VTE patients with high generalizability.

The demographic characteristics of TROLL, including median age and sex distribution, are comparable to those of other VTE registries from Western countries.[9,13–17] The proportion of unprovoked VTE in TROLL is in line with two other large Norwegian population-based studies,[18,19] as well as studies of unselected patients with VTE from the United States and Europe.[9,14,20] In TROLL, 22.5% of the patients with VTE have active cancer, which corresponds well to other large studies reporting proportions within the range of 20%–25% with active cancer.[3,9,14,19,21,22]

One of the major strengths of TROLL is the close follow-up of VTE outcomes. Since TROLL recruits patients from a single site, all participants have been managed according to the same standardized management procedures with regards to diagnosis, treatment, and follow-up. If an adverse outcome occurs during follow-up, the patient will most likely to be admitted to Østfold Hospital, given that they still reside in the area. TROLL's linkage to the National Population Registry ensures continuous update on death or migration out of the hospital's catchment area, and follow-up can be terminated upon the date of migration or death. TROLL collects follow-up data on bleeding, VTE recurrence, and mortality, and since TROLL started in 2005, some patients already have over 15 years of follow-up data. This is a clear advantage compared to the registries with shorter follow-up periods ranging from 30 days to 5 years.[9,14,16,17,23–27]

Other VTE registries include only PE and DVT,[14,16,17,23,25,27] or are restricted to PE.[24,26] The Computerized Registry of Patients with Venous Thromboembolism (RIETE) has only recently started to enroll superficial, splanchnic, retinal, and cerebral thrombosis in addition to PE and DVT.[9] TROLL includes all types of VTE, and enrollment of understudied subgroups will provide important baseline and follow-up data for future research.

Since the establishment of TROLL, there has been a paradigm shift in anticoagulation treatment of VTE from VKAs to DOACs. Consequently, TROLL provides follow-up data from both treatment eras. In 2020, 73% of the patients with VTE in TROLL received DOACs, and the proportion of patients treated with DOACs will likely continue to increase. As TROLL recruits unselected patients treated in regular clinical practice within a modern and well-organized health care system, new drugs or management strategies introduced in the future will be reflected in and made available for research in the TROLL registry.

Data on concomitant medications, cancer treatment information, and other comorbidities are not registered in TROLL. However, one of TROLL's advantages is the possibility to link data to other local registries (e.g., the hospital's ICD-10 registry, laboratory data system, radiology imaging system, and electronic medical charts) as well as national registries (e.g., the Norwegian Prescription Database, the Norwegian Patient Registry, and the Cancer Registry of Norway). This provides unique opportunities for studying a wide range of intermediate exposures and long-term outcomes. In addition, the biobank will enable important research on biomarkers for

TABLE 4 Distribution of anticoagulant treatment for overall VTE and by VTE localization

	Total *n* = 4975	PE *n* = 2689	DVT *n* = 2023	UEDVT *n* = 123	Splanchnic *n* = 127	Cerebral sinus vein *n* = 13
LMWH, *n* (%)	1513 (30.4)	955 (35.5)	431 (21.3)	45 (36.6)	82 (64.5)	0 (0)
VKA, *n* (%)	1505 (30.3)	759 (28.2)	697 (34.5)	26 (21.1)	11 (8.7)	12 (92.3)
DOAC, *n* (%)	1957 (39.3)	975 (36.2)	895 (44.2)	52 (42.3)	34 (26.8)	1 (7.7)
Rivaroxaban	1256 (25.2)	519 (19.3)	700 (34.6)	26 (21.1)	11 (8.7)	0 (0)
Apixaban	681 (13.7)	444 (16.5)	190 (9.4)	24 (19.5)	22 (17.3)	1 (7.7)
Edoxaban	13 (0.3)	7 (0.3)	4 (0.2)	1 (0.8)	1 (0.8)	0 (0)
Dabigatran	7 (0.1)	5 (0.2)	1 (0.05)	1 (0.8)	0 (0)	0 (0)

Abbreviations: DOAC, direct oral anticoagulants; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; UEDVT, upper-extremity DVT; VKA, vitamin K antagonist.

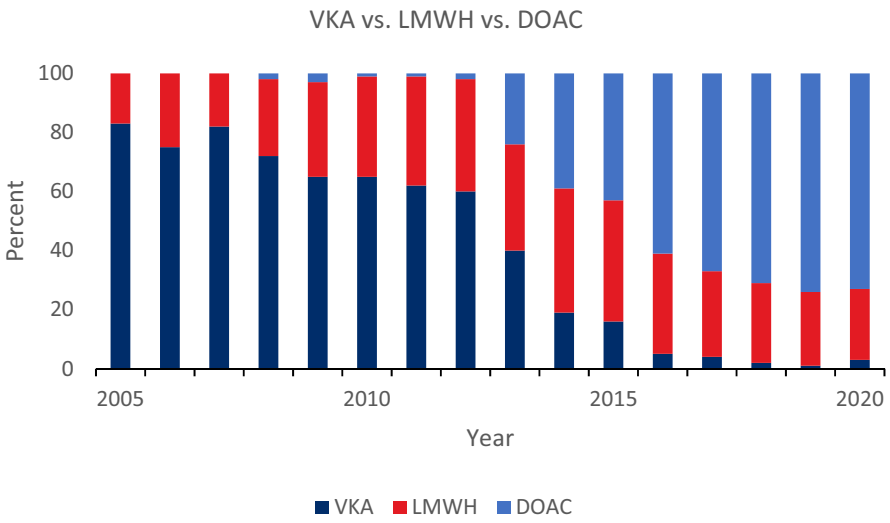


FIGURE 3 Annual proportion of VTE cases treated with vitamin K antagonist (VKA), low-molecular-weight heparin (LMWH) and direct oral anticoagulants (DOAC), respectively

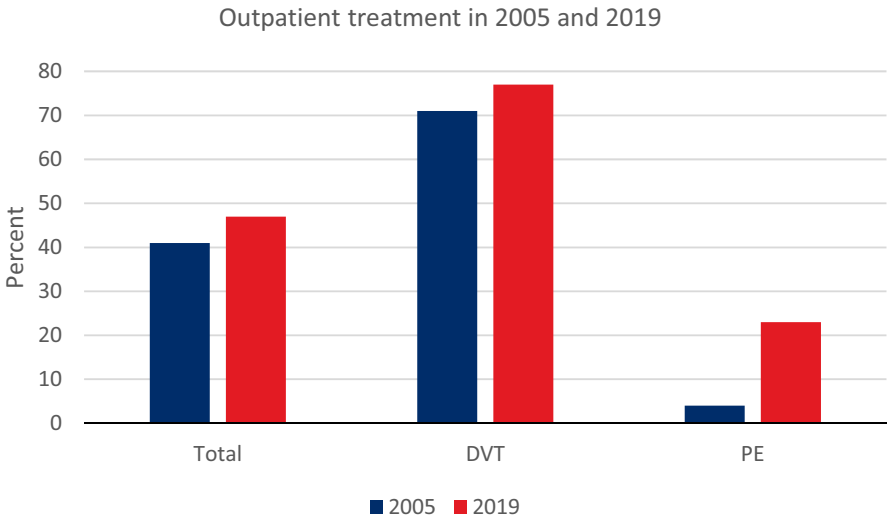


FIGURE 4 Proportion of patients with venous thromboembolism, deep vein thrombosis (DVT), and pulmonary embolism (PE) treated solely in the outpatient clinic in 2005 and 2019

risk stratification and pathophysiological mechanisms of future adverse outcomes.

Other applications of TROLL include the possibility of identifying and recruiting patients to clinical trials. To date, TROLL has been used to identify and select patients eligible for several clinical studies.[8,28,29]

In addition to all types of VTE, TROLL also includes superficial vein thromboses (SVT) with 360 SVT registered to date. These are not included in this report. However, there is an opportunity to study diagnosis, management, and outcomes after SVT in the future.

The TROLL registry has some limitations. First, data that had not been systematically collected by the treating nurse or

physician and that had not been recorded in the electronic medical records were not registered and would hence be classified as missing. Examples of variables with a high proportion of missing values in the registry are BMI and VTE in first-degree relatives. In total, 80% of the participants were included in a face-to-face visit, while 20% were identified by review of medical records. This may have led to missing data regarding some of the variables. Second, if a patient is admitted to another hospital with a bleeding event or recurrent VTE during follow-up, this event might be missed in TROLL. However, patients who are still alive and reside in the catchment area will likely be followed up by Østfold Hospital after such an adverse event. Information related to this event can be retrieved from the other hospital(s) to update the TROLL registry at a later visit. Finally, the registry lacks information on ethnic and sociocultural background. However, the study population comprised predominantly Caucasians (more than 90%), and our results may therefore not be generalizable to populations with a higher ethnic diversity. Data on sociocultural bakground can be acquired through linkage with national registries.

In conclusion, TROLL is a relatively large ongoing, population-based registry of unselected patients with VTE, with high-quality data that represent a valuable source of real-world data on the management and outcomes of VTE. The findings to date, including demographics, clinical features, risk factors, and classification of VTE correspond well with those reported from other registries. The close, long-term follow-up of patients in TROLL, combined with collection of biobank material and linkage to other local and national registries, provide unique opportunities for research on VTE in the future.

AUTHOR CONTRIBUTIONS

C.T.J. participated in patient inclusion, data collection, study conception and design, statistical analysis, interpretation of results, and drafting the manuscript. W.G. established the registry and was responsible for study conception and design and interpretation of results. M.T. and S.K.B. participated in study conception and design, choice of statistical analysis, and interpretation of results. H.H.P., E.F., and E.T. participated in patient inclusion, updating of the registry, and data collection. C.R. and M.K.O. were responsible for regulatory approvals. J.G., A.G.G., and S.F.V. participated in the design of the registry, data collection, updating, and interpretation of results. All authors participated in reviewing the manuscript and approved the final version of the manuscript.

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RELATIONSHIP DISCLOSURE

W.G. reports fees for participation in the Advisory Board from Amgen, Novartis, Pfizer, Principia Biopharma Inc–a Sanofi Company, Sanofi, SOBI, Griffols, UCB, and Argenx; lecture honoraria from Amgen, Novartis, Pfizer, Bristol Myers Squibb, SOBI, Griffols, and Sanofi; and research grants from Bayer and BMS/Pfizer. E.T. reports lecture honoraria from BMS, Pfizer, Bayer, Alexion, Novartis, and Janssen. All other authors disclose no conflicts of interest.

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