Rationale, Design and Methodology of the Computerized Registry of Patients with Venous Thromboembolism (RIETE)

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Abstract

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a preventable cause of in-hospital death, and one of the most prevalent vascular diseases. There is a lack of knowledge with regards to contemporary presentation, management and outcomes of patients with VTE. Many clinically important subgroups (including the elderly, those with recent bleeding and pregnant patients) have been under-represented in clinical trials. Furthermore, design of clinical trials is challenging in some scenarios, such as in those with hemodynamically unstable PE. RIETE (*Registro Informatizado Enfermedad TromboEmbolica*) is a large prospective multinational ongoing registry, designed to address these unmet needs using representative data from multiple centres. Initiated in Spain in 2001, RIETE currently includes 179 centres in 24 countries and has enrolled more than 72,000 patients. RIETE has helped characterize the pattern of

Keywords

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presentation and outcomes of VTE, including the aforementioned understudied subgroups. RIETE has recently expanded to collect long-term outcome data, and has broadened its inclusion criteria to enrol other forms of venous thrombosis (such as cerebral vein thrombosis and splanchnic vein thrombosis). The RIETE platform is also being used to conduct pragmatic comparative effectiveness studies, including randomized trials. Future steps would focus on collaboration with additional centres across the world, and efforts to ensure the quality and expansion of the registry. In conclusion, RIETE is a large ongoing registry of patients with VTE and other thrombotic conditions. Its results could be helpful for improving our understanding of the epidemiology, patterns of care and outcomes of patients with thrombotic disease.

Introduction

Venous thromboembolism (VTE) is an important preventable cause of in-hospital death.^{1–3} VTE including deep vein thrombosis (DVT) and pulmonary embolism (PE) afflicts an estimated 1,000,000 new cases annually in Europe and the United States, combined.^{4–6} Among survivors, VTE is associated with recurrent events, post-thrombotic syndrome, pulmonary hypertension and bleeding events (as a result of anticoagulant therapy), all of which contribute to the high burden of the disease.^{7,8}

However, contemporary aspects of VTE presentation, pattern of care, and outcomes are understudied. Published epidemiological studies are generally limited by small size, data age (representing a different era of diagnosis and treatment)^{9,10} or lack of detailed clinical data.^{11,12} Clinical trials have also faced challenges in providing adequate evidence base, with ethical and feasibility issues limiting recruitment for some important conditions (e.g. PE with hemodynamic instability, or VTE among those with recent bleeding),¹³ and underrepresentation of many key subgroups (such as the elderly, pregnant patients, and those with high risk of bleeding) that limit the availability and generalizability of the evidence. These issues have led to a growing unmet imperative for evidence from large groups of patients without numerous exclusions.¹⁴ Contemporary information to characterize the modern-day presentation, risk factor profile, treatment and outcomes of patients can inform practice and policy, preventing unnecessary harm, and bringing novel hypotheses for future research and improving quality and outcomes.^{15–18}

The *Registro Informatizado Enfermedad TromboEmbolica* (RIETE) is a large prospective registry initiated to address these unmet needs and has been enrolling patients with objectively confirmed VTE since 2001. Several of the resultant studies have provided a better understanding of the epidemiology,^{19,20} common treatment patterns,^{21,22} and outcomes^{23,24} of patients with VTE and the key understudied clinical subgroups.^{25–27} In response to continued and expanding investigations from RIETE, herein we provide an overview of the design, methodology, possible and future directions of the registry.

Methods

RIETE is an ongoing, prospective multicentre multinational observational study of patients with objectively confirmed

acute VTE. The registry was originally started in Spain in 2001 with the goal of gathering a large sample of patients with VTE, with specific attention to those excluded from the typical randomized trials of anticoagulant therapy (e.g. those with severe renal insufficiency, liver failure, recent major bleeding, pregnancy, disseminated cancer, thrombocytopenia and the elderly) with an aim to understand their common presentation, management pattern and outcomes, as well as factors associated with better or worse patient outcomes. The hope was also to use the hypothesis-generating findings to help design new randomized clinical studies.

With successful recruitment of an increasing number and diversity of patients over time, the numbers of retrieved variables and data elements were progressively increased. The platform, including the electronic data entry system, was translated to English from 2006 and the network expanded to other participating centres. As of June 30, 2017, RIETE includes 207 investigators from 179 participating centres. RIETE is registered at Clinicaltrials.gov (NCT: 02832245). Detailed information about participating centres is also available at the registry Web site: <https://www.riete.org/>.

Patients, Inclusion and Exclusion Criteria

At each participating site, patients are screened by the site investigators and checked for eligibility (►Table 1). All patients are objectively confirmed with acute symptomatic or asymptomatic VTE (i.e. DVT, PE, or both). More recently, in an attempt to similarly understand the presentation, treatment pattern, and outcomes of other thrombotic conditions, RIETE has also started to enrol patients with superficial vein thrombosis, splanchnic vein thrombosis (i.e. thrombosis involves the mesenteric, splenic or portal veins), retinal vein thrombosis and cerebral vein thrombosis. At each participating centre, every attempt is made to enrol consecutive patients and RIETE investigators are committed, by contract agreement, to enrol consecutive patients. Periodic audits of the sites have confirmed consecutiveness. Further, comparison against the Spanish Ministry of Health database has shown that patients in RIETE have similar characteristics to the data from all-comers with VTE in that database.²⁸ No duplicate entries are permitted and patients who are enrolled in blinded treatment trials are ineligible.

Methods of DVT diagnosis include contrast venography, ultrasonography, magnetic resonance or, rarely in the past,

Table 1 Inclusion and exclusion criteria for RIETE

Inclusion criteria
Acute objectively confirmed DVT or acute objectively confirmed PE ^{a,b}
Availability of data for at least 54 core variables and minimum of 3-mo follow-up
Exclusion criteria
Enrolment in any treatment trial (VTE or other conditions) in a blinded fashion
Previous enrolment in the registry
Lack or withdrawal of patient consent

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; RIETE, Registro Informatizado Enfermedad TromboEmbolica (also known as the Computerized Registry of Patients with Venous Thromboembolism); VTE, venous thromboembolism.

^aNot mutually exclusive (i.e. patients may have both DVT and PE but will not be double counted).

^bIn more recent years, those with superficial vein thrombosis, splanchnic vein thrombosis (i.e. thrombosis involves thrombosis in the mesenteric, splenic or portal veins), retinal vein thrombosis and cerebral vein thrombosis have been separately enrolled.

plethysmography (only 172 patients in the entire cohort). PE is diagnosed on the basis of pulmonary angiography, contrast-enhanced computed tomography (CT) of the chest (specifically CT pulmonary angiography), lung scintigraphy or rarely on the basis of confirmed DVT in patients with signs and symptoms of PE.

RIETE, by design, does not currently enrol patients with intracardiac thrombi in the absence of VTE. As of 30 June 2017, a total of 72,107 valid patients with acute VTE have been enrolled in RIETE. Currently, RIETE has 179 participating sites from 24 countries and across 3 continents. There has been a growth, over time, in the number of involved sites and countries (►Fig. 1A, B).

Data Elements

Key data elements in RIETE include demographics, VTE risk factors and comorbidities (such as presence or absence of immobility, hormonal therapies, pregnancy and puerperal state, recent surgery, active cancer, heart failure, chronic lung

disease, renal and liver function, prior VTE, prior bleeding episodes, dementia, depression, autoimmune disorders, gastroduodenal ulcer, inflammatory bowel disease and others). It also includes concomitant medications (such as antiplatelet agents, corticosteroids, nonsteroidal anti-inflammatory drugs, erythropoietin, statins and psychotropic drugs) and disposition status (inpatient vs. outpatient). Test results (common blood tests [including plasma haematocrit, platelet count, creatinine and others], cardiac biomarkers [including troponin, CK-MB and B-type natriuretic peptide], electrocardiography [including the rhythm, presence of right bundle branch block, S1Q3T3 pattern and others], ultrasonography, echocardiography, CT scan) and therapies (including antithrombotic medications and advanced therapies such as thrombolytic therapy, surgical thrombectomy and inferior vena caval filter placement; ►Table 2) are separately recorded.

Outcomes

The main outcomes of interest in RIETE include all-cause death, PE-specific death, recurrent DVT, recurrent PE, major bleeding, non-major (but clinically relevant) bleeding, arterial ischemic events (myocardial infarction, ischemic stroke or leg amputation), thrombocytopenia, bone fractures and other side-effects of the prescribed therapies. In recent years, development of post-thrombotic syndrome (since 2008) and chronic thromboembolic pulmonary hypertension (since 2015) are also ascertained in those with reported long-term follow-up (►Table 3). RIETE, by design, does not require universal screening for asymptomatic events.

Follow-up

The minimum follow-up duration for patients in RIETE is at least 3 months.¹³ Since 2010, collaborators have been requested to extend follow-up to at least 12 months. As for June 30 2017, a total of 24,828 patients have followed up for at least 12 months and 11,304 for at least 24 months (►Fig. 2).

Ethics

All enrollees provide written or verbal informed consent according to the local ethics protocols of enrolling centres. The institutional review board at each enrolling centre approves participation in RIETE for the site investigators and allows the entry of de-identified patient information into the RIETE database.

Fig. 1 Participating countries in RIETE in 2001 (A) and 2017 (B).

Table 2 Select list of data elements

	Patients with available values (N)	DVT cohort	PE cohort	Other patients ^a	Total
Patients (%)	72,107	33,150	35,745	3,212	72,107 (100%)
Disposition (inpatient vs. outpatient)	70,122	8,228 (25.5%)	10,872 (31.3%)	794 (25.4%)	19,894 (28.4%)
Demographics					
Male (%)	72,107	17,019 (51.3%)	16,668 (46.6%)	1,684 (52.4%)	35,371 (49.1%)
Age (y ± SD)	72,107	63.5 ± 18	67.3 ± 17	63.5 ± 15.4	65.4 ± 17.5
Body mass index (kg/m ²)	50,118	27.6 ± 5.2	28.2 ± 5.7	27 ± 5.2‡	27.8 ± 5.5
Underlying conditions					
Chronic lung disease	72,107	2,800 (8.4%)	5,112 (14.3%)	326 (10.1%)	8,238 (11.4%)
Chronic heart failure	72,107	1,455 (4.4%)	3,263 (9.1%)	137 (4.3%)	4,855 (6.7%)
Diabetes	45,033	2,778 (14.8%)	3,693 (16%)	585 (18.7%)	7,056 (15.7%)
Hypertension	45,263	8,117 (43%)	11,869 (51%)	1,409 (44.9%)	21,395 (47.3%)
Prior myocardial infarction	45,002	1,224 (6.5%)	1,918 (8.3%)	176 (5.7%)	3,318 (7.4%)
Prior ischemic stroke	44,981	1,095 (5.8%)	1,800 (7.8%)	170 (5.5%)	3,065 (6.8%)
Recent major bleeding	72,107	678 (2%)	836 (2.3%)	125 (3.9%)	1,639 (2.3%)
Anaemia	72,107	11,883 (35.8%)	11,680 (32.7%)	1,410 (43.9%)	24,973 (34.6%)
Platelet count <150,000	71,990	885 (2.7%)	823 (2.3%)	144 (4.6%)	1,852 (2.6%)
Platelet count >450,000	71,990	1,113 (3.4%)	1,264 (3.5%)	155 (4.9%)	2,532 (3.5%)
Recent surgery	72,107	3,476 (10.5%)	4,241 (11.9%)	316 (9.8%)	8,033 (11.1%)
Recent immobility	72,107	7,530 (22.7%)	7,642 (21.4%)	464 (14.4%)	15,636 (21.7%)
Active cancer	72,107	7,655 (23.1%)	7,974 (22.3%)	1,612 (50.2%)	17,241 (23.9%)
Prior VTE	72,107	5,336 (16.1%)	5,258 (14.7%)	272 (8.5%)	10,866 (15.1%)
Pregnancy/Puerperium	72,107	561 (1.7%)	314 (0.9%)	31 (1%)	906 (1.3%)
Hormonal use	72,107	1,779 (5.4%)	1,916 (5.4%)	158 (4.9%)	3,853 (5.3%)
Initial therapy					
Low-molecular-weight heparin	72,107	30,634 (92.4%)	30,138 (84.3%)	2,504 (78%)	63,276 (87.8%)
Unfractionated heparin	72,107	877 (2.6%)	3413 (9.5%)	94 (2.9%)	4,384 (6.1%)
Fondaparinux	72,107	736 (2.2%)	613 (1.7%)	92 (2.9%)	1,441 (2%)
NOACs	20,792	579 (7.1%)	417 (4%)	35 (1.6%)	1,031 (5.0%)
Thrombolytic therapy	72,107	54 (0.2%)	882 (2.5%)	3 (0.1%)	939 (1.3%)
Vena cava filter use	72,107	720 (2.2%)	1,042 (2.9%)	80 (2.5%)	1,842 (2.6%)
Clinical presentation					
SBP levels <90 mm Hg	69,286	268 (0.9%)	1,253 (3.5%)	37 (1.3%)	1,558 (2.2%)
Syncope	69,108	195 (0.6%)	5,211 (15%)	46 (1.6%)	5,452 (7.9%)
Heart rate ≥110 mm Hg	67,212	1,374 (4.6%)	7,272 (21%)	169 (6.1%)	8,815 (13.1%)
Sat O ₂ levels <90%	27,097	289 (6.9%)	6,618 (29.6%)	64 (12%)	6,971 (25.7%)

Abbreviations: DVT, deep vein thrombosis; NOAC, non-vitamin K antagonist oral anticoagulant; PE, pulmonary embolism; VTE, venous thromboembolism.

Note: Data include patients enrolled until 30 June 2017.

^aThose with superficial vein thrombosis, splanchnic vein thrombosis (i.e. thrombosis involves thrombosis in the mesenteric, splenic or portal veins), retinal vein thrombosis and cerebral vein thrombosis.

Table 3 Main study outcomes and their definitions

Outcomes	Definition
All-cause mortality	
PE-specific mortality	Autopsy-confirmed. In the absence of autopsy, fatal PE is defined as any death appearing within 10 d after symptomatic PE diagnosis, in the absence of any alternative cause of death
Recurrent VTE	Recurrent DVT is defined as a new non-compressible vein segment, or an increase of the vein diameter of >4 mm compared with the last available measurement on venous ultrasonography. Recurrent PE is defined as a new ventilation–perfusion mismatch on lung scan or a new intraluminal filling defect on spiral computed tomography or pulmonary angiography
Major bleeding	Bleeding events that are overt and required a transfusion of two units or more of blood, or are retroperitoneal, spinal or intracranial, or when they are fatal
Clinically relevant non-major bleeding	Bleeding events that are overt and require medical assistance but not fulfilling criteria for major bleeding
Fatal bleeding	Any death occurring within 10 d of a major bleeding episode, in the absence of an alternative cause of death
Post-thrombotic syndrome	Evaluated every 12 mo according to the Villalta score
Chronic thromboembolic pulmonary hypertension	Diagnosed by site investigators based on assessment of clinical information and tests including echocardiography, ventilation–perfusion lung scan, pulmonary angiography, pulmonary functional tests and right heart catheterization
Bone fractures	Confirmed by adequate image testing
Myocardial infarction	Presence of typical chest pain in combination with a transient increase of creatine kinase-MB or troponin and/or typical electrocardiographic signs (development of pathologic Q-waves or ST-segment elevation or depression) that are not otherwise explained
Arterial ischemic events	Diagnosed in the setting of acute neurological event not resolving completely within 24 hours, confirmed by computed tomography or magnetic resonance imaging

Abbreviations: PE, pulmonary embolism; VTE, venous thromboembolism.

Note: Outcomes are assessed in various time intervals including during the inpatient stay, 30 days after the event, 3 months after the event and longer term in a subset of patients with available data.

Fig. 2 Cumulative number of enrolled patients over time. The top-five recruiting countries are Spain ($n = 54,525$), Italy ($n = 5,910$), France ($n = 4,233$), Israel ($n = 2,650$) and Switzerland ($n = 1,144$). (A) Cumulative number of enrolled patients over time. (B) Amount of patients followed-up for >3, 6, 9, 12, 15, 18 and 24 months.

Data Entry

Data are entered into electronic case report forms through an electronic portal and submitted to the coordinating centre via secure Web site¹³ (► Fig. 3, <https://www.riete.org/login.php>).

Quality Control and Oversight

S & H Medical Science Service serves as the coordinating centre for RIETE. The study coordinating centre assigns a unique identification number for each patient to avoid duplicate entries and ensure the security of protected health information. The coordinating centre ensures the completeness of data entry by site investigators. In order for a patient to count in the registry, a minimum of 54 core data elements (variables) related to the first 3 months of care need to be completed. Of the main items in these 54 elements, age, gender, weight, date of diagnosis, recent major bleeding, characteristics of DVT/PE (diagnostic method), risk factors (cancer, surgery, immobilization, history of DVT/PE, pregnancy), laboratory (haemoglobin, leukocytes, platelets), clinical symptoms, treatments (drug, dose, onset and finishing date), IVC filter use (yes/no and timing), date of last follow-up and events (death, thromboembolic recurrence, bleeding) could be named. The number of variables has been progressively increasing over the years. Recently, depending on the events, ancillary tests, therapies and follow-up duration, each patient may be represented by up to 1,000 variables filled out; yet as discussed earlier, there are only 54 core mandatory variables per patient. Data quality is electronically monitored by S & H Medical Science Service on

Computerized Registry of Patients with Venous Thromboembolism (RIETE)

My patients | Reports | Analyzers | Download Database | RIETE Info | Help | Exit

Baseline | Diagnosis | Risk Factors | Laboratory | Treatment | Follow-up | Sequelae | CTEPH

Patient 1000-0190 **Record data** **Valid patient**
(Click over the button to see the errors)

Baseline **Concomitant Diseases**

Inclusion date: 14-11-2016

Gender: Female

Age: years

Race: NOT SPECIFIED

Weight: Kg

Height: cm

Waist circumference: cm

General Comments on the patient:

In/outpatient: NOT SPECIFIED

Heart rate: beats/min

Systolic blood pressure: mmHg

Respiratory rate: respiratory rate/minute

Concomitant diseases at the time of VTE diagnosis?: NOT SPECIFIED

Concomitant therapy: NOT SPECIFIED

Admission to hospital: NOT SPECIFIED

Date of diagnosis: (dd-mm-yyyy)

Date of hospital discharge: (dd-mm-yyyy)

Did the patient suffer any major bleeding in the past month?: NOT SPECIFIED

Fig. 3 Screenshot from the electronic data entry platform.

a weekly basis. In case of identification of several inconsistencies from any enrolling centre, a full audit of all the data from that centre is performed. In addition, trained staffs from S & H Medical Science Service make periodic visits to participating centres and compare the information in a randomly selected sample of patients entered by the site investigators. In the most recent audit, RIETE staff assessed 4,100 randomly chosen records that included 1,230,000 measurements. The data showed 95% overall agreement between the registered information by site investigators and patients' original records (with no difference between key data elements and others, and no specific patterns that undermined a group of variables disproportionately). The audits also included ascertainment of inclusion of consecutive patients via cross-checking by available medical records at enrolling hospitals. The RIETE leadership and steering committee (led by Dr. Monreal) is in charge of overseeing the registry, ensuring the collaboration between the investigators and the S & H Medical Science Service, and proposing, soliciting and overseeing the process for develop-

ment, and publication of new research projects based on RIETE. All active members are permitted to propose new studies. The proposals are reviewed by the leadership and steering committee and, if not overlapping with prior or ongoing projects, would be enlisted.

Statistical Analysis

A dedicated team of statisticians conducts the statistical analyses. The main data warehouse for RIETE is in Madrid, Spain, and managed by S & H Medical Science Service. RIETE analyses are either performed by statisticians at the S & H Medical Science Service or by other RIETE statisticians who have signed confidentiality contracts and downloaded de-identified portions of the data into secure platforms. Patients whose entered data do not fulfil the minimum available variables criteria will not be entered in any of the analyses. Categorical variables are reported as frequencies and percentages. Continuous variables are reported as means with standard deviation. Tests of comparison, association, survival analysis, multivariable

adjustment, propensity-score matching and others are contingent on hypotheses and questions per each individual study from the RIETE database. Large numbers would enable the investigators to explore the regional variations, and to determine the robustness of analyses by factors such as sites and volume. Multi-level modelling could help minimize errors related to potential clustering of observations, if one occurs at certain centres. Although RIETE does not have a study-wide statistical approach for missing data (e.g. multiple imputations), the coordinating centre makes study-wide efforts to help minimize missing data elements by frequent communications with each of the enrolling centres.

Discussion

RIETE is a large multicentric multinational registry of patients with acute VTE. Over the past 15 years, it has provided data for more than 100 original research studies, some of which have been among the seminal studies related to epidemiology, prognostication or comparative effectiveness of strategies for management of VTE.^{19,21,29–31} Investigations from RIETE have provided novel information about VTE risk factors, therapies and outcomes among understudied subgroups such as pregnant patients, those at high risk of bleeding, those with morbid obesity and the elderly persons.^{25,26,32,33} Other studies revealed distinct risk gradients across key subgroups, including differential presentation and outcomes based on primary cancer site.³⁴ Some others provided evidence from observational studies in areas where randomized trials are extremely difficult to conduct, if not impossible, including for those with VTE and high bleeding risk,^{24,35} or patients with PE and hypotension.²³ RIETE investigators have also contributed to studies related to prognostication, including for the simplified PE severity index.²⁹ Other studies have shown the contemporary trends in hospitalizations, clinical presentation and outcomes of patients with DVT and with PE.^{21,22} With continued enrolment and increase in the number and diversity of collaborating centres, in part via better recognition of the registry by other investigators and in part by active advocacy from existing RIETE investigators and the steering committee, it is expected that the registry continues to provide a greater breadth and depth of information related to presentation, treatment pattern and outcomes of patients with VTE.

There are several functions in the usage of registries for cardiovascular conditions^{15–17} including VTE. Registries enable us to look into VTE epidemiology (including hospitalizations, and in many cases outpatients), common treatment patterns, trends, variations in practice and also to address some questions related to comparative effectiveness, especially in areas where randomized trials are unfeasible or unlikely to occur (including efficacy studies related to the oldest old, patients with morbid obesity or severe renal insufficiency, or for conditions where equipoise is questioned because of existing grandfathered therapies, or where enrolment is technically challenging because of the high acuity of medical illness [such as the case of massive PE, disseminated cancer and others]; ► **Table 4**).^{36–42} Registry data complement

the findings from randomized trials and are a critical element for contemporary knowledge generation, and quality control. Findings can reflect on routine practice results for newly approved or existing health interventions and may unravel new signals for benefits or harms that were previously understudied in randomized trials. Further, they can reflect on variations in care, temporal trends over time and adherence to guidelines recommendations, among many other utilities.

RIETE encompasses several distinct features¹⁸ compared with other existing and ongoing VTE registries.^{10,36–38,42} The large sample size (to our knowledge, the largest prospective patient-level VTE registry) enables the investigators to study questions that are not feasibly addressed in single-centre studies.^{19,21,29–31} Patient enrolment is from many centres with various levels of acuity of care, making it a representative sample and providing opportunities for evaluation of care in ambulatory setting, general hospitals, and centres of excellence. Other future specific areas of interest include (but are not limited to) identification of risk factor profiles related to VTE recurrence that can help determine the duration of anticoagulation, and identification of factors based on VTE presentation and comorbidities that could provide hints at tailored therapy for specific drugs, doses and duration (which would be subsequently tested in trial platforms). RIETE also plans to provide additional empiric evidence on non-vitamin-K antagonist oral anticoagulants. Although such patients are currently under-represented in the registry, in part because of slow uptake of this class in Spain due to reimbursement issues, with increasing enrolment of patients from the rest of the world, and possibility of adjustments in the reimbursement regulations in Spain, we anticipate that the breadth and depth of data related to this class of medications in RIETE will be further enriched. The registry also aims to pay attention to understudied subgroups of patients such as those with splanchnic vein thrombosis, superficial vein thrombosis and others. RIETE is gaining additional information to help better characterize the significance and risk factor profile for long-term complications, such as post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension. Furthermore, unlike several other registries, continuation of the registry over time makes it possible for assessment of temporal trends. Finally, the platform will also bring possibilities for future patient-oriented research investigations related to VTE, including pragmatic intervention trials,⁴³ and quality improvement initiatives. In fact, some such randomized trials are under way using the RIETE platform.^{44–46} In large part driven by the data from the RIETE and tools created based on original such data, RIETE investigators have also created Web site that provides information related to VTE for physicians and patients, including risk estimation models (<http://trombo.info/?lang=en>). Also, contrary to some of the other existing registries, despite receiving funding from various groups, RIETE is independently investigator driven. The data are entirely managed by the investigators. The funders (including industry funders) have no rights in reviewing the protocols, abstracts or manuscripts, or about decisions to submit them.

Table 4 Summary information about some of the large VTE registries and their key features

	Setting	Enrolment timeline	Study population (DVT, PE, VTE)	Sample size	Follow-up period	Main objectives
MASTER ³⁶	25 centres from Italy	January 2002 to October 2004	Adults with objectively confirmed VTE	2,111	All patients were followed up for 24 mo. Patient management was at the discretion of the attending physicians	To describe the demographics, risk factors, clinical features and outcomes of patients with VTE during short-term and long-term follow-up
EMPEROR ³⁷	Emergency departments from 22 academic and community hospitals in the United States	January 2005 to December 2008	Adults with objectively confirmed PE	1,880	Main follow-up was up to 30 d	To define the presenting symptoms, signs, risk factor profile, treatments (including use of anticoagulants) and short-term outcomes of patients with PE presenting to emergency departments
IPER ³⁸	47 hospitals from Italy	September 2006 to 2010	Adults with objectively confirmed PE	1,716	NA, follow-up ended in August 2014	Similar to MASTER (see above)
SWIVTER ³⁹	18 hospitals in Switzerland	January 2009 to May 2010	Adults with objectively confirmed VTE	1,247	No systematic follow-up beyond hospital discharge	A study to determine characteristics of patients with VTE, and key subgroups, including the elderly, and those with cancer
VTEval ⁴⁰	Started as a single-centre study in Germany with plan to involve more centres	April 2013 to ongoing	Adults with objectively confirmed VTE	2,000 planned, unclear details	Active follow-up is planned for 36 mo	To determine the symptoms, risk factors as well as psychosocial, environmental and lifestyle factors associated with VTE. The study is also collecting blood samples for future 'omics' studies, on genome, transcriptome, proteome, metabolome and phenotype
PREFER in VTE ⁴¹	381 centres from 7 European countries	January 2013 to July 2014	Adults with objectively confirmed VTE	3,545	Up to 12 mo (by phone calls)	To determine the clinical characteristics, management and outcomes, and also health care resource utilization and costs of care for 12 mo of treatment
GARFIELD-VTE ⁴²	500 sites from 28 countries	July 2014 to ongoing	Adults with objectively confirmed acute VTE	10,000 planned, recruitment recently completed	Minimum follow-up for 36 mo	To describe the global treatment patterns and outcomes for VTE. Utilization and outcomes of patients receiving non-vitamin K antagonist oral anticoagulants, descriptions about regional variations in care and description of long-term outcomes such as post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension could be named
RIETE	179 centres from 24 countries	2001 to ongoing	Adults with objectively confirmed VTE. In recent years, also enrolling patients with thrombosis at unusual sites	72,107 patients as of June 2017. Still recruiting	Minimum follow-up for 3 mo, but many have longer follow-up (see ► Fig. 1B)	Detailed in the text. In brief, to describe the epidemiology, treatment patterns and outcomes of a large group of patients with VTE, including many of the understudied subgroups. Also to provide a platform for several additional investigations, including pragmatic trials

Abbreviations: EMPEROR, Emergency Medicine Pulmonary Embolism in the Real World Registry; GARFIELD, Global Anticoagulant Registry in the FIELD; IPER, Italian Pulmonary Embolism Registry; MASTER, Multicenter Advanced Study for a Thromboembolism Registry; NA, not available; PE, pulmonary embolism; SWIVTER, SWISS Venous Thromboembolism Registry; VTE, venous thromboembolism.

Note: Only dedicated VTE registries with > 1,000 patients are discussed. The list is not meant to be exhaustive and did not include several of the registries from the prior years.

In conclusion, RIETE is a large existing and ongoing VTE registry. It is expected that RIETE will continue to provide clinical evidence for understudied subgroups with thrombotic disease, and will have more prominent role for facilitation of multicentre (and multinational studies) that could be used for assessment of variations and disparities in care, quality improvement and conducting comparative effectiveness research. The overarching goal is to improve the management of VTE through better understanding of prevention, as well as demographics, comorbidities, treatment patterns and outcomes of patients with VTE.

Source of Funding and Its Roles

RIETE is an investigator-initiated registry. During the first 5 years, it was supported by Red Respira from the Instituto Carlos III, Spain (Red Respira-ISCIII-RTIC-03/11).¹³ It has been also supported by Sanofi Spain in Spain and by Bayer Pharma AG for the rest of the world. There is no payment per recruited patient. The main incentive for patients and investigators participating in RIETE is to generate new knowledge to help for better understanding of VTE epidemiology and outcomes. None of the sponsors have had any role in the design of the registry and do not have rights to access the database, or to review or comment on pre-published studies from RIETE.

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