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 Informado 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

► venous thrombosis
► deep vein thrombosis
► pulmonary embolism
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. 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.

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), or lack of detailed clinical data. 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), 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.

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.

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, common treatment patterns, and outcomes of patients with VTE and the key understudied clinical subgroups. 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.

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,
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, gastro-duodenal 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. Since 2010, collaborators have been requested to extend follow-up to at least 12 months. As of 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.

Table 1 Inclusion and exclusion criteria for RIETE

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute objectively confirmed DVT or acute objectively confirmed PE</td>
</tr>
<tr>
<td>Availability of data for at least 54 core variables and minimum of 3-mo follow-up</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Exclusion criteria</th>
</tr>
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<tbody>
<tr>
<td>Enrolment in any treatment trial (VTE or other conditions) in a blinded fashion</td>
</tr>
<tr>
<td>Previous enrolment in the registry</td>
</tr>
<tr>
<td>Lack of withdrawal of patient consent</td>
</tr>
</tbody>
</table>

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.

In 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.

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.

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Fig. 1 Participating countries in RIETE in 2001 (A) and 2017 (B).
### Table 2 Select list of data elements

<table>
<thead>
<tr>
<th></th>
<th>Patients with available values (N)</th>
<th>DVT cohort</th>
<th>PE cohort</th>
<th>Other patients&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients (%)</strong></td>
<td>72,107</td>
<td>33,150</td>
<td>35,745</td>
<td>3,212</td>
<td>72,107 (100%)</td>
</tr>
<tr>
<td><strong>Disposition</strong></td>
<td>70,122</td>
<td>8,228 (25.5%)</td>
<td>10,872 (31.3%)</td>
<td>794 (25.4%)</td>
<td>19,894 (28.4%)</td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>72,107</td>
<td>17,019 (51.3%)</td>
<td>16,668 (46.6%)</td>
<td>1,684 (52.4%)</td>
<td>35,371 (49.1%)</td>
</tr>
<tr>
<td>Age (y ± SD)</td>
<td>72,107</td>
<td>63.5 ± 18</td>
<td>67.3 ± 17</td>
<td>63.5 ± 15.4</td>
<td>65.4 ± 17.5</td>
</tr>
<tr>
<td><strong>Body mass index (kg/m²)</strong></td>
<td>50,118</td>
<td>27.6 ± 5.2</td>
<td>28.2 ± 5.7</td>
<td>27 ± 5.2‡</td>
<td>27.8 ± 5.5</td>
</tr>
<tr>
<td><strong>Underlying conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>72,107</td>
<td>2,800 (8.4%)</td>
<td>5,112 (14.3%)</td>
<td>326 (10.1%)</td>
<td>8,238 (11.4%)</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>72,107</td>
<td>1,455 (4.4%)</td>
<td>3,263 (9.1%)</td>
<td>137 (4.3%)</td>
<td>4,855 (6.7%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>45,033</td>
<td>2,778 (14.8%)</td>
<td>3,693 (16%)</td>
<td>585 (18.7%)</td>
<td>7,056 (15.7%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>45,263</td>
<td>8,117 (43%)</td>
<td>11,869 (51%)</td>
<td>1,409 (44.9%)</td>
<td>21,395 (47.3%)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>45,002</td>
<td>1,224 (6.5%)</td>
<td>1,918 (8.3%)</td>
<td>176 (5.7%)</td>
<td>3,318 (7.4%)</td>
</tr>
<tr>
<td>Prior ischemic stroke</td>
<td>44,981</td>
<td>1,095 (5.8%)</td>
<td>1,800 (7.8%)</td>
<td>170 (5.5%)</td>
<td>3,065 (6.8%)</td>
</tr>
<tr>
<td>Recent major bleeding</td>
<td>72,107</td>
<td>678 (2%)</td>
<td>836 (2.3%)</td>
<td>125 (3.9%)</td>
<td>1,639 (2.3%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>72,107</td>
<td>11,883 (35.8%)</td>
<td>11,680 (32.7%)</td>
<td>1,410 (43.9%)</td>
<td>24,973 (34.6%)</td>
</tr>
<tr>
<td>Platelet count &lt; 150,000</td>
<td>71,990</td>
<td>885 (2.7%)</td>
<td>823 (2.3%)</td>
<td>144 (4.6%)</td>
<td>1,852 (2.6%)</td>
</tr>
<tr>
<td>Platelet count &gt; 450,000</td>
<td>71,990</td>
<td>1,113 (3.4%)</td>
<td>1,264 (3.5%)</td>
<td>155 (4.9%)</td>
<td>2,532 (3.5%)</td>
</tr>
<tr>
<td>Recent surgery</td>
<td>72,107</td>
<td>3,476 (10.5%)</td>
<td>4,241 (11.9%)</td>
<td>316 (9.8%)</td>
<td>8,033 (11.1%)</td>
</tr>
<tr>
<td>Recent immobility</td>
<td>72,107</td>
<td>7,530 (22.7%)</td>
<td>7,642 (21.4%)</td>
<td>464 (14.4%)</td>
<td>15,636 (21.7%)</td>
</tr>
<tr>
<td>Active cancer</td>
<td>72,107</td>
<td>7,655 (23.1%)</td>
<td>7,974 (22.3%)</td>
<td>1,612 (50.2%)</td>
<td>17,241 (23.9%)</td>
</tr>
<tr>
<td>Prior VTE</td>
<td>72,107</td>
<td>5,336 (16.1%)</td>
<td>5,258 (14.7%)</td>
<td>272 (8.5%)</td>
<td>10,866 (15.1%)</td>
</tr>
<tr>
<td>Pregnancy/Puerperium</td>
<td>72,107</td>
<td>561 (1.7%)</td>
<td>314 (0.9%)</td>
<td>31 (1%)</td>
<td>906 (1.3%)</td>
</tr>
<tr>
<td>Hormonal use</td>
<td>72,107</td>
<td>1,779 (5.4%)</td>
<td>1,916 (5.4%)</td>
<td>158 (4.9%)</td>
<td>3,853 (5.3%)</td>
</tr>
<tr>
<td><strong>Initial therapy</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Low-molecular-weight heparin</td>
<td>72,107</td>
<td>30,634 (92.4%)</td>
<td>30,138 (84.3%)</td>
<td>2,504 (78%)</td>
<td>63,276 (87.8%)</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>72,107</td>
<td>877 (2.6%)</td>
<td>3413 (9.5%)</td>
<td>94 (2.9%)</td>
<td>4,384 (6.1%)</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>72,107</td>
<td>736 (2.2%)</td>
<td>613 (1.7%)</td>
<td>92 (2.9%)</td>
<td>1,441 (2%)</td>
</tr>
<tr>
<td>NOACs</td>
<td>20,792</td>
<td>579 (7.1%)</td>
<td>417 (4%)</td>
<td>35 (1.6%)</td>
<td>1,031 (5%)</td>
</tr>
<tr>
<td>Thrombolytic therapy</td>
<td>72,107</td>
<td>54 (0.2%)</td>
<td>882 (2.5%)</td>
<td>3 (0.1%)</td>
<td>939 (1.3%)</td>
</tr>
<tr>
<td>Vena cava filter use</td>
<td>72,107</td>
<td>720 (2.2%)</td>
<td>1,042 (2.9%)</td>
<td>80 (2.5%)</td>
<td>1,842 (2.6%)</td>
</tr>
<tr>
<td><strong>Clinical presentation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP levels &lt; 90 mm Hg</td>
<td>69,286</td>
<td>268 (0.9%)</td>
<td>1,253 (3.5%)</td>
<td>37 (1.3%)</td>
<td>1,558 (2.2%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>69,108</td>
<td>195 (0.6%)</td>
<td>5,2112 (15%)</td>
<td>46 (1.6%)</td>
<td>5,452 (7.9%)</td>
</tr>
<tr>
<td>Heart rate ≥ 110 mm Hg</td>
<td>67,212</td>
<td>1,374 (4.6%)</td>
<td>7,272 (21%)</td>
<td>169 (6.1%)</td>
<td>8,815 (13.1%)</td>
</tr>
<tr>
<td>Sat O&lt;sub&gt;2&lt;/sub&gt; levels &lt; 90%</td>
<td>27,097</td>
<td>289 (6.9%)</td>
<td>6,618 (29.6%)</td>
<td>64 (12%)</td>
<td>6,971 (25.7%)</td>
</tr>
</tbody>
</table>

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.

<sup>a</sup>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.
Data Entry

Data are entered into electronic case report forms through an electronic portal and submitted to the coordinating centre via secure Web site\(^ {13}\) (– 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

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Definition</th>
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<tbody>
<tr>
<td>All-cause mortality</td>
<td>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</td>
</tr>
<tr>
<td>PE-specific mortality</td>
<td>Recurrent DVT is defined as a new non-compressible vein segment, or an increase of the vein diameter of &gt;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</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>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</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>Bleeding events that are overt and require medical assistance but not fulfilling criteria for major bleeding</td>
</tr>
<tr>
<td>Clinically relevant non-major bleeding</td>
<td>Any death occurring within 10 d of a major bleeding episode, in the absence of an alternative cause of death</td>
</tr>
<tr>
<td>Post-thrombotic syndrome</td>
<td>Evaluated every 12 mo according to the Villalta score</td>
</tr>
<tr>
<td>Chronic thromboembolic pulmonary hypertension</td>
<td>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</td>
</tr>
<tr>
<td>Bone fractures</td>
<td>Confirmed by adequate image testing</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>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</td>
</tr>
<tr>
<td>Arterial ischemic events</td>
<td>Diagnosed in the setting of acute neurological event not resolving completely within 24 hours, confirmed by computed tomography or magnetic resonance imaging</td>
</tr>
</tbody>
</table>

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 even 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.
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 audits 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 development, 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 fulfill 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. 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. Other studies revealed distinct risk gradients across key subgroups, including differential presentation and outcomes based on primary cancer site. 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, or patients with PE and hypertension. RIETE investigators have also contributed to studies related to prognostication, including for the simplified PE severity index. Other studies have shown the contemporary trends in hospitalizations, clinical presentation and outcomes of patients with DVT and with PE. 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 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 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 and quality improvement initiatives. In fact, some such randomized trials are under way using the RIETE platform. 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.

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**Table 4.** RIETE investigators have also contributed to studies related to prognostication, including for the simplified PE severity index. Other studies have shown the contemporary trends in hospitalizations, clinical presentation and outcomes of patients with DVT and with PE. 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 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 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 and quality improvement initiatives. In fact, some such randomized trials are under way using the RIETE platform. 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

<table>
<thead>
<tr>
<th>Setting</th>
<th>Enrolment timeline</th>
<th>Study population (DVT, PE, VTE)</th>
<th>Sample size</th>
<th>Follow-up period</th>
<th>Main objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>MASTER(^{36})</td>
<td>25 centres from Italy January 2002 to October 2004</td>
<td>Adults with objectively confirmed VTE</td>
<td>2,111</td>
<td>All patients were followed up for 24 mo. Patient management was at the discretion of the attending physicians</td>
<td>To describe the demographics, risk factors, clinical features and outcomes of patients with VTE during short-term and long-term follow-up</td>
</tr>
<tr>
<td>EMPEROR(^{37})</td>
<td>Emergency departments from 22 academic and community hospitals in the United States January 2005 to December 2008</td>
<td>Adults with objectively confirmed PE</td>
<td>1,880</td>
<td>Main follow-up was up to 30 d</td>
<td>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</td>
</tr>
<tr>
<td>IPER(^{38})</td>
<td>47 hospitals from Italy September 2006 to 2010</td>
<td>Adults with objectively confirmed PE</td>
<td>1,716</td>
<td>NA, follow-up ended in August 2014</td>
<td>Similar to MASTER (see above)</td>
</tr>
<tr>
<td>SWIVTER(^{39})</td>
<td>18 hospitals in Switzerland January 2009 to May 2010</td>
<td>Adults with objectively confirmed VTE</td>
<td>1,247</td>
<td>No systematic follow-up beyond hospital discharge</td>
<td>A study to determine characteristics of patients with VTE, and key subgroups, including the elderly, and those with cancer</td>
</tr>
<tr>
<td>VTEval(^{40})</td>
<td>Started as a single-centre study in Germany with plan to involve more centres April 2013 to ongoing</td>
<td>Adults with objectively confirmed VTE</td>
<td>2,000 planned, unclear details</td>
<td>Active follow-up is planned for 36 mo</td>
<td>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 phenome</td>
</tr>
<tr>
<td>PREFER in VTE(^{41})</td>
<td>381 centres from 7 European countries January 2013 to July 2014</td>
<td>Adults with objectively confirmed VTE</td>
<td>3,545</td>
<td>Up to 12 mo (by phone calls)</td>
<td>To determine the clinical characteristics, management and outcomes, and also health care resource utilization and costs of care for 12 mo of treatment</td>
</tr>
<tr>
<td>GARFIELD-VTE(^{42})</td>
<td>500 sites from 28 countries July 2014 to ongoing</td>
<td>Adults with objectively confirmed acute VTE</td>
<td>10,000 planned, recruitment recently completed</td>
<td>Minimum follow-up for 36 mo</td>
<td>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</td>
</tr>
<tr>
<td>RIETE</td>
<td>179 centres from 24 countries 2001 to ongoing</td>
<td>Adults with objectively confirmed VTE. In recent years, also enrolling patients with thrombosis at unusual sites</td>
<td>72,107 patients as of June 2017. Still recruiting</td>
<td>Minimum follow-up for 3 mo, but many have longer follow-up (see (\text{Fig. 1B}))</td>
<td>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</td>
</tr>
</tbody>
</table>

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-RITC-03/11). 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.

Acknowledgments
We express our gratitude to Sanofi Spain for supporting this Registry with an unrestricted educational grant. We also express our gratitude to Bayer Pharma AG for supporting this Registry. Bayer Pharma AG’s support was limited to the part of RIETE outside Spain, which currently accounts for a 24.45% of the total patients included in the RIETE Registry. We also thank Silvia Galindo, S & H Medical Science Service, for the statistical analysis of the data presented in this paper. We are grateful to the RIETE investigators who are the driving force of this registry, and patients who agreed and continue to agree to participate in RIETE without whose support this work would have never been possible. Dr. Bikdeli is supported by the National Heart, Lung, and Blood Institute, National Institutes of Health, through grant number T32 HL007854. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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Appendix A

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