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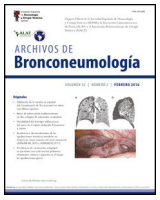

Editorial

RIETE Registry: Past, Present and Future

Registro RIETE: Pasado, presente y futuro

Start of the RIETE Registry

Venous thromboembolism (VTE) is the third most common vascular disease. However, numerous knowledge gaps exist with respect to disease epidemiology, treatment patterns, and patient outcomes. Randomized trials play an integral role in assessing the efficacy of selected health interventions. However, numerous other questions continue to persist for epidemiology, comparative effectiveness in patients excluded from randomized trials (e.g., pregnant women, the very elderly, those with renal or liver insufficiency), or for policy.[1] The RIETE (Registro Informatizado de Enfermedad TromboEmbólica) registry was formed in 2001, initially in an attempt to learn the natural history of VTE in patients with special conditions, and how to prevent and treat it better.[2]

Expansion of RIETE: summary of methods

With successful patient recruitment and continued contributions to the literature and practice, RIETE expanded the data elements being captured, type of diseases being studied, and the network of enrolling centers. As of June, 2021, RIETE includes 241 investigators from 224 participating centers in 27 countries. RIETE is registered at Clinicaltrials.gov (NCT:02832245).

Patients are excluded only if they are currently participating in a clinical trial with a blinded medication. All patients provide informed consent for their participation in the registry, according to the requirements of the ethics committee within each hospital. Patients are managed according to the clinical practice of each participating hospital. After the initial diagnosis, patients are followed-up for ≥3 months, with many patients having 1-year follow-up available. Data quality is regularly monitored electronically, including checks to detect inconsistencies or errors and periodic visits to participating hospitals by the RIETE coordinating center (S&H Medical Sciences). In response to continued and expanding investigations from RIETE, herein we provide an overview of some of the most relevant studies so far.

Main Findings from RIETE in the Past Two Decades

The main domains of RIETE studies are summarized in Table 1.

VTE epidemiology

As for the epidemiology of VTE, we performed numerous studies in patients that are often excluded from randomized clinical trials, such as pregnant patients, or those with recent major bleeding, disseminated cancer, renal or liver insufficiency, among others.[3–8] In our experience, one in every 5 patients with VTE (19%) had at least one of the exclusion criteria to be recruited in the pivotal randomized trials with direct oral anticoagulants.[1] Not unexpectedly, patients with exclusion criteria had a 4-fold higher rate of major bleeding (and a 6-fold higher rate of fatal bleeding) than those without exclusion criteria. Moreover, patients with exclusion criteria also had a 3-fold higher rate of VTE recurrences (and a 4-fold higher rate of fatal PE) than those without exclusion criteria.

Outcomes research

Among 39,257 patients with acute PE, we found that admission to high volume hospitals (>40 PEs per year) was associated with significant reductions in adjusted PE-related mortality at 30 days.[9] In another study, we found that patients with PE had better outcomes if they were acutely managed according to international guidelines.[10] We also explored the imaging modalities used in patients with PE.[11] CT-scan was the dominant modality (78%). A greater proportion of patients underwent ventilation/perfusion scanning in larger hospitals compared with smaller hospitals. The use of CT-scan varied between 13.3% and 98.3% across the countries, and its use increased over time.

Comparative effectiveness studies

We compared the 15- and 30-day outcomes in VTE patients receiving enoxaparin twice daily vs. once daily.[12] On propensity analysis, patients on enoxaparin once daily had significantly fewer major bleeds and fewer deaths than those on enoxaparin twice daily. In VTE patients weighing > 100 kg, we compared the association between the use of capped doses (18,000 IU/d) of low-molecular-weight heparin (LMWH) vs. uncapped doses (>18,000 IU/d).[13] Multivariable analyses confirmed that patients receiving capped doses had lower rates of the composite of VTE recurrences, major bleeding or death.

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Table 1
Completed studies and future directions on several topics.

	Completed RIETE studies	Future Directions
VTE Epidemiology	Recent major bleeding. Of 6,361 patients enrolled in 2004, 170 (2.7%) had experienced major bleeding < 30 days before VTE: gastrointestinal 69, intracranial 60, other 41.[3] Only patients with less than 14 days from bleeding to VTE had an increased risk for re-bleeding or death. Cancer. Among 10,962 patients with cancer and VTE, 2.2% died of PE and 1.6% died of bleeding during the first 12 months.[4] In patients initially presenting with PE, fatal PE was 3-times more common than fatal bleeding. In those with only DVT, fatal PE was 3-times less common than fatal bleeding. In another study, the rate of VTE recurrences during anticoagulation was similar to the rate of major bleeding in patients with breast or colorectal cancer.[5] In patients with prostate cancer, the rate of recurrences was half the rate of major bleeding, whereas in patients with lung cancer the rate of recurrences was over 2-fold higher than the rate of major bleeding. Pregnancy. Among 596 pregnant and 523 postpartum women with VTE, PE was less common in pregnant vs. postpartum women (27% vs. 42%).[6] Pregnant women were most commonly treated with low molecular weight heparin (73% vs. 29%), and received more vena cava filters (6.0% vs. 4.2%) than women with postpartum. By 90 days, one pregnant woman died of bleeding and one postpartum woman died of PE. Elderly patients. Of 13,011 patients enrolled up to 2005, 22% were aged ≥80 years. During the first 3 months, the 3.4% rate of major bleeding in patients aged ≥80 years exceeded the 2.1% rate of VTE recurrences, but the 3.7% rate of fatal PE outweighed the 0.8% rate of fatal bleeds.[7] The rate of fatal PE was 2.5-times higher than the rate of fatal bleeding in patients aged < 80 years, but was 4.4-times lower in those aged ≥ 80 years. Renal insufficiency. Among 10,526 patients with VTE, 88% had creatinine clearance levels > 60 mL/min; 6.7% had 30–60 mL/min; and 5.6% had < 30 mL/min.[8] The rate of fatal PE within 15 days was: 1.0%, 2.6%, and 6.6%, respectively, and fatal bleeding was: 0.2%, 0.3%, and 1.2%. Our data confirmed a high rate of bleeding in patients with renal insufficiency, but the 6.6% rate of fatal PE far exceeded the 1.2% rate of fatal bleeding.	With increasing numbers of patients, we will better know the subgroups. We will apply machine learning methods to identify at risk patients. We will compare the rates of VTE recurrences vs. major bleeds in all cancer sites, and according to the presence of metastases. With increasing numbers of patients we will improve existing knowledge on the optimal diagnosis and treatment in pregnant women with VTE. We will apply machine learning methods to identify at risk patients for VTE recurrences and for major bleeding. We will apply machine learning methods to identify at risk patients for fatal PE and for major bleeding.
Outcomes research	Hospital volume and outcomes. Among 39,257 patients with acute PE, admission to high volume hospitals (>40 PEs per year) was associated with significant reductions in adjusted PE-related mortality at 30 days.[9] Adherence to guidelines. Patients with PE had better outcomes if they were acutely managed according to international guidelines.[10] Variations in diagnostic tests. We explored the imaging modalities used in patients with PE, and found variations in their use according to patient or institutional factors and over time.[11]	We will use data visualization methods to share our findings with the community.
Comparative effectiveness studies	Once vs. twice daily enoxaparin. We compared the outcomes in 3,786 VTE patients receiving initial therapy with enoxaparin twice daily and 944 once daily.[12] On propensity analysis, patients on enoxaparin once daily had significantly fewer major bleeds at 15 and at 30 days, and also fewer deaths at 15 and at 30 days than those on enoxaparin twice daily. Capped doses of LMWH in the obese. 2,846 patients who weighed >100 kg were studied: 16% received capped doses of LMWH (18,000 IU/d) as initial therapy.[13] Multivariable analysis confirmed that patients receiving capped doses had lower rates of the composite of VTE recurrences, major bleeding or death.	We will compare outcomes in patients receiving recommended vs. non-recommended doses of anticoagulants, and in other clinical scenarios.

Registry-based randomized trials

The RIETE platform brings 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.

Future directions

It is expected that in the future RIETE will continue to provide clinical evidence for understudied subgroups with VTE, and will have more prominent role for facilitation of multicenter (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 the demographics, comorbidities, risk factors, and utilization of appropriate therapies for patients with VTE.

Conflict of interest

Dr. Bikdeli reports that he is a consulting expert, on behalf of the plaintiff, for litigation related to two specific brand models of IVC filters.

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