

Editorial Focus

Newly diagnosed venous thromboembolism: Which patients will bleed after anticoagulation is initiated?

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Randomized controlled trials represent the pinnacle of evidence-based medicine. Yet, they have a myriad of problems that limit their applicability in the daily clinical practice. Most serious is the obligatory long list of exclusion criteria. This feature tends to sterilize the results by eliminating high-risk patients with multisystem morbidities. As a consequence, bleeding and clotting adverse event rates in randomized controlled trials of thromboembolism tend to be low. These unrealistic results are often "too good to be true" and leave clinicians wondering how best to interpret the findings. Randomized trials are also usually unwieldy because they require an inordinate amount of time to design, initiate, and complete. Often they are marred by slower than predicted enrollment or inadequate power to provide a definitive answer to the fundamental question being posed. To ensure proper safeguards for patients, these trials consume investigators' resources quickly at extreme expense.

Fortunately, observational studies based upon patient registries complement the results of randomized clinical trials. Observational studies can be marred by unrecognized confounding that skews the results. The patient population and outcomes can change over time. But observational studies do reflect "the real world." When designed and analyzed rigorously, patient registry trials can enhance our fund of knowledge and provide a foundation for improved clinical practice.

In the field of venous thromboembolism, the RIETE (Registro Informatizado de Enfermedad Tromboembolica) investigators provide the model for excellence in observational studies. RIETE began in 2001 as a tool to improve our understanding of how to treat patients with deep vein thrombosis (DVT) and pulmonary embolism (PE) who are ordinarily excluded from clinical trials, such as those with chronic kidney disease, pregnancy, and major bleeding. So far, more than 22,000 patients have been enrolled in RIETE and have completed three months of follow-up. The Principal Investigator of this enterprise is Manuel Monreal, MD. Core staff includes three informatics personnel responsible for the integrity and updates of the website, two clinical coordinators, one statistician, one medical writer, two Quality Control experts, and two individuals who travel to audit

the quality of the data from participating sites. The epicenter is Spain, but the effort has spread to France, Italy, Israel, Greece, Denmark, Brazil, and Argentina. The Spanish Ministry of Health and Sanofi-Aventis provide funding, but the Steering Committee and Adjudication Committee are independent. And RIETE investigators maintain complete control of publication policy.

The RIETE investigators have enjoyed well deserved productivity. Beginning in 2003, they have published 30 original reports. As a Section Editor, I am pleased that *Thrombosis and Haemostasis* has featured some of their important contributions. In this month's issue, Ruiz-Gimeinez et al. have tackled a difficult and vexing clinical question (1). Which patients with acute venous thromboembolism will suffer major bleeding complications over the ensuing three months of anticoagulation? The question is of enormous importance because intensive anticoagulation is the cornerstone of management for patients with newly diagnosed DVT or PE. At the moment, we use "gestalt" to make educated guesses about which patients are most likely to develop important haemorrhage. We lack a quantitative or semi-quantitative tool to assist us in rendering our judgment.

Our clinical impression of the degree of bleeding risk is of crucial importance. If we declare that a patient is at too high a risk of bleeding to safely tolerate anticoagulation, the plan of action will usually lead to placement of an inferior vena caval filter. The filter is a potentially life-saving device to prevent major PE, but it will not halt the thrombotic process and will not prevent the development of larger, more proximal DVT.

In the United States, filter placement to manage acute DVT has become pandemic. In a registry of 5,451 patients from 183 United States study sites, 781 (14%) underwent inferior vena caval filter placement (2). It is not clear how many filters were warranted, because criteria for assessing bleeding risk have remained murky.

RIETE has studied predictive variables for major bleeding in a *tour de force*. They utilized a derivation sample of 13,057 and a validation sample of 6,572 patients with acute venous thromboembolism. In both groups, 47% had clinically overt PE. Only 2% received inferior vena caval filters. Ninety were treated in-

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initially with low-molecular-weight heparin, and 8% received unfractionated heparin, mostly as a bridge to warfarin. During the first three months after diagnosis, the overall death rate was 8.3% in the derivation sample and 8.2% in the validation sample. Both groups had a fatal bleeding rate of 0.6%. The frequency of major non-fatal bleeding was 2.6% in the derivation sample and 2.7% in the validation sample.

In the derivation sample, the investigators applied univariate and then multivariate analysis for major bleeding. This permitted them to construct a point score system to predict future major bleeding:

- Recent major bleeding: 2 points
- Creatinine > 1.2 mg/dl: 1.5 points
- Haemoglobin < 13 g/dl for men and < 12 g/dl for women: 1.5 points
- Cancer: 1 point
- Clinically overt pulmonary embolism: 1 point
- Age > 75 years: 1 point

References

1. Ruiz-Giménez N, Suárez C, González R, et al. Predictive variables for major bleeding events in patients presenting with documented acute venous thromboembolism. Findings from the RIETE Registry. *Thromb Haemost* 2008; 100: 26-31.
2. Jaff MR, Goldhaber SZ, Tapson VF. High utilization rate of vena cava filters in deep vein thrombosis. *Thromb Haemost* 2005; 93: 1117-1119.

When they applied the clinical score to the derivation sample and validation sample, the results were remarkably similar. This facilitated the creation of a semiquantitative bleeding risk index classification:

- Low risk: 0 points
- Intermediate risk: 1–4 points
- High risk: > 4 points

The implications of this point score system are profound. One-third of the major bleeding cases were fatal. The most frequent sites of major bleeding were gastrointestinal (34%), muscular (15%), genitourinary (12%), and brain (11%).

I know that I will carry this semi-quantitative bleeding risk index classification with me when I assess newly diagnosed venous thromboembolism patients. Those at highest risk have at least a 5% chance of developing major bleeding complications. Such patients may be appropriate for inferior vena caval filter placement. Conversely, there may be patients at low or intermediate point score risk in whom the initial “gestalt” feeling is for filter placement. Data from RIETE suggest that this large group of patients might best be served by cautious initiation of anticoagulation.