Venous thromboembolism in patients with special conditions – editorial

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Current guidelines on antithrombotic therapy provide a critical review of the literature related to the management of patients with venous thromboembolism (VTE) and lay the scientific groundwork for the standard of care, based largely on data from randomized controlled clinical trials (1). However, a number of VTE patients are often excluded from randomized clinical trials (for example due to pregnancy, renal insufficiency or high risk of bleeding). Thus, there is little evidence on what would be the best therapeutic approach for these patients.

The Registro Informatizado de Enfermedad TromboEmbólica (RIETE Registry) is an ongoing, international, prospective registry of consecutive patients with acute VTE designed to gather and analyze data on treatment patterns and outcomes in patients with acute VTE. It started in Spain in 2001, and 6 years later the database was translated into English with the aim to expand the Registry to other countries, ultimately allowing physicians worldwide to use the database. In contrast to a randomized controlled trial, there is no imposed experimental intervention: the management is determined solely by physicians. Thus, it provides data on patients with VTE in a real-world situation with an unselected patient population. It can, therefore, help to identify practices for providing treatment to patients and factors associated with better or worse patient outcomes. Data from RIETE are hypothesis-generating and provide feedback from real-world clinical situations which may be of help when designing new randomized clinical studies.

Participating physicians ensure that eligible patients are consecutively enrolled. Data are recorded on to a computer-based case report form at each participating hospital and submitted to a centralized coordinating center through a secure website. The study coordinating center assigns a unique identification number to patients to maintain their confidentiality and is responsible for all data management. Data quality is regularly monitored electronically, including checks to detect inconsistencies or errors, which are resolved by contacting the local coordinators. Data quality is also monitored by periodic visits to participating hospitals by contract research organizations that compare the information in medical records with the submitted data in the website.

Consecutive patients with acute deep vein thrombosis (DVT) or pulmonary embolism (PE), confirmed by objective tests, are enrolled. Patients are excluded only if they are currently participating in a therapeutic clinical trial with a blind medication. All patients provide informed consent to 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 (i.e., there is no standardization of treatment). The drug, dose and duration of therapy are recorded. During each visit, any signs or symptoms suggesting VTE recurrences, bleeding complications, and any other adverse events are noted. After initial diagnosis, patients are followedup for at least three months, but there is no limit for the duration of follow-up.

RIETE is an independent registry, supported by Sanofi-Aventis in Spain and by Bayer Pharma AG outside Spain. During the first five years, RIETE was also supported by Red Respira from the Instituto Carlos III, Spain (Red Respira-ISCiii-RTIC-03/11). Neither Sanofi-Aventis nor Bayer Pharma AG have any right to access the database, and there is no payment per recruited patient.

Of 6,855 patients enrolled in February 2004, 1635 (24 %) had at least one reason to be excluded from randomized clinical trials: recent bleeding 2.6 %; renal insufficiency 14 %; thrombocytopenia 2.5 %; abnormal prothrombin time 9.1 %; and pregnancy 0.7 % (2). During the 3-month follow-up period, the rates of fatal PE (odds ratio [OR]: 3.3; 95 % CI: 2.5–5.2); major bleeding (OR: 3.1; 95 % CI: 2.3–4.1) and fatal bleeding (OR: 4.1; 95 % CI: 2.1–8.0) were significantly higher in patients with at least one of these co-morbidities than in the remaining 5,220 patients.

Patients with major bleeding who subsequently develop acute VTE pose a particularly difficult therapeutic dilemma because they are perceived to be at substantial risk of re-bleeding if therapy with anticoagulants is prescribed, and of recurrent PE in the absence of treatment. Of 6361 patients enrolled up to January 2004, 170 (2.7 %) had experienced recent major bleeding (3). Only patients with less than 14 days from bleeding to VTE had an increased risk for re-bleeding (hazard ratio [HR]: 2.4; 95 % CI: 1.2–5.0) or death (HR: 2.8; 95 % CI: 1.8–4.5). Moreover, we found that insertion of a vena cava filter was independently associated with a lower incidence of fatal bleeding (OR: 0.10; 95 % CI: 0.01–0.79) and all-cause mortality (OR: 0.21; 95 % CI: 0.07–0.63) (4). Finally, in 141 patients presenting with VTE <30 days after intracranial bleeding we found that all fatal PEs had occurred during the first week, thus suggesting that the intensity of anticoagulant therapy (at least during the first week) should be higher (5).

In a study involving 173 pregnant women, 135 postpartum and 798 contraceptive users, we found that 44 % of contraceptive users but only 22 % of pregnant women presented with clinically overt PE (6). Interestingly, only a minority (2.0 %) of those presenting with PE had hypoxemia. During the 3-month study period, three women died of PE, two of them during the first few hours after arriving to the emergency ward, with no time to start any therapy. They had no associated co-morbidities, and probably would not have died if they had not developed VTE. We thus suggest that the non-specific nature of PE signs may have caused some delay in PE diagnosis and initiation therapy.

The risk of dying from PE or bleeding during the treatment of DVT, and whether these risks are influenced by patient age, has been reported in 16 199 patients with acute DVT of the lower limbs (7). We found that in patients aged 60 years or older the risk of fatal bleeding was 0.70 % and that of fatal PE was 0.22 %. Although the relative risk of having a fatal bleed versus

a fatal PE was the same during the first week of treatment (0.12 % vs. 0.10 %), fatal bleeding was more frequent than fatal PE subsequently (0.59 % vs. 0.12 %). The much higher risk of dying from bleeding than from PE after the first week suggests that a less aggressive anticoagulant strategy might reduce fatal bleeding more than it would increase fatal PE during this period.

In patients with severe renal failure, current guidelines on antithrombotic therapy suggest that unfractionated heparin should be preferred over LMWH, and that LMWH should be administered with care and the dose adjusted to anti-Xa level, or using half the recommended dose (1). Up to March 2005, 10526 patients with acute VTE were enrolled, of whom 9234 (88 %) had creatinine clearance (CrCl) levels > 60 mL/min; 704 (6.7 %) had CrCl 30–60 mL/min; and 588 (5.6 %) had < 30 mL/min (8). The incidence of fatal PE within 15 days was: 1.0 %, 2.6 % and 6.6 %, respectively. Fatal bleeding appeared in 0.2 %, 0.3 %, and 1.2 %, respectively. Our data confirm an increased incidence of bleeding events in patients with renal insufficiency, but their 6.6 % incidence of fatal PE far exceeded their 1.2 % rate of fatal bleeding. Hence, our data support the use of full-dose anticoagulant therapy in patients with severe renal insufficiency.

RIETE has several limitations. First, patients are not treated with a standardized anticoagulant regimen; treatment varies with local practice, and is likely to be influenced by a physician's assessment of a patient's risk of bleeding. Second, to fulfil the definition of fatal PE in RIETE, patients must first experience an objectively confirmed PE event, followed by death within 10 days. Thus, all sudden unexplained deaths which are usually considered as "likely" fatal recurrent PE are not considered, and the rate of fatal PE may have been underestimated, especially after hospital discharge. Third, RIETE is an ongoing observational registry (and not a randomized controlled trial), and the data are hypothesis-generating. Thus, we should be extremely cautious before suggesting changes in treatment strategies based on uncontrolled registry data. Finally, there is no monitoring and no external control of the data entered in RIETE, and there is also no external adjudication of the events, which are merely reported by the authors. Strengths of the registry include that a large number of consecutive unselected patients are enrolled and a large number of variables are considered.

Our data suggest that the information gathered in RIETE may be a useful basis for future controlled clinical trials investigating modified anticoagulant regimens vs standard therapy in special VTE populations. Moreover, our data provide information on the epidemiology of VTE in different countries, and might be useful in monitoring the efficacy and safety of new anticoagulants in the near future.

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