Outcomes during anticoagulation in patients with symptomatic vs. incidental splanchnic vein thrombosis

Antonella Tufano, Walter Ageno, Pierpaolo Di Micco, Alferio Niglio, Vladimir Rosa, Aitor Ballaz, Andrei Braester, Carmen Mª. Rubio, Virginia Isern, Egidio Imbalzano, Manuel Monreal, the RIETE Investigators

PII: S0049-3848(18)30215-9
DOI: doi:10.1016/j.thromres.2018.02.143
Reference: TR 6965

To appear in: *Thrombosis Research*

Received date: 15 November 2017
Revised date: 17 January 2018
Accepted date: 21 February 2018

Please cite this article as: Antonella Tufano, Walter Ageno, Pierpaolo Di Micco, Alferio Niglio, Vladimir Rosa, Aitor Ballaz, Andrei Braester, Carmen Mª. Rubio, Virginia Isern, Egidio Imbalzano, Manuel Monreal, the RIETE Investigators , Outcomes during anticoagulation in patients with symptomatic vs. incidental splanchnic vein thrombosis. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. Tr(2017), doi:10.1016/j.thromres.2018.02.143

Outcomes during anticoagulation in patients with symptomatic vs. incidental splanchnic vein thrombosis.

Antonella TUFANO, MD. PhD. Regional Reference Centre for Coagulation Disorders. Department of Clinical Medicine and Surgery. Federico II University Hospital. Naples. Italy.

Walter AGENO, MD. Department of Medicine and Surgery. University of Insubria. Varese. Italy.

Pierpaolo DI MICCO, MD. PhD. Department of Internal Medicine and Emergency Room. Ospedale Buon Consiglio Fatebenefratelli. Naples. Italy.

Alferio NIGLIO, MD. Department of Internal Medicine. Second University of Naples. Naples. Italy.

Vladimir ROSA, MD. PhD. Department of Internal Medicine. Hospital Universitario Virgen de Arrixaca. Murcia. Spain.

Aitor BALLAZ, MD. Department of Pneumonology. Hospital de Galdakao. Vizcaya. Spain.

Andrei BRAESTER, MD. Department of Haematology. Galilee Medical Center. Nahariya. Israel.

Carmen Mª RUBIO, MD. Department of Internal Medicine. Hospital Alto Guadalquivir Andújar. Jaén. Spain.

Virginia ISERN, MD. Department of Internal Medicine. Hospital Dos de Maig. Barcelona. Spain.

Egidio IMBALZANO, MD. Department of Clinical and Experimental Medicine. A.O.U Policlinico "G. Martino". Messina. Italy.

Manuel MONREAL, MD. Ph.D. Department of Internal Medicine. Hospital Germans Trias i Pujol. Badalona, Barcelona. Universidad Católica de Murcia. Spain.

And the RIETE Investigators*
*A full list of the RIETE investigators is given in the appendix

Short title: Outcome in patients with splanchnic vein thrombosis.

Corresponding author: Dr. Antonella Tufano MD, Ph.D.
Regional Reference Centre for Coagulation Disorders. Department of Clinical Medicine and Surgery. Federico II University Hospital. Naples. Italy.

e-mail address: atufano@unina.it
Phone number: +39 3337394490

Funding:Sanofi Spain, Bayer Pharma AG

Abstract.

Introduction: Current guidelines recommend the use of anticoagulant therapy in patients with symptomatic splanchnic vein thrombosis (SVT) and suggest no routine anticoagulation in those with incidental SVT**.**

Methods: We used the RIETE (Registro Informatizado Enfermedad Trombo Embólica) registry to assess the rate and severity of symptomatic venous thromboembolism (VTE) recurrences and major bleeding events appearing during the course of anticoagulation in patients with symptomatic or incidental SVT.

Results: In March 2017, 521 patients with SVT were recruited. Of them, 212 (41%) presented with symptomatic SVT and 309 had incidental SVT. Most (93%) patients received anticoagulant therapy (median, 147 days). During the course of anticoagulation, 20 patients developed symptomatic VTE recurrences (none died) and 26 had major bleeding (fatal bleeding, 5). On multivariable analysis, patients with incidental SVT had a non-significantly higher risk for symptomatic VTE recurrences (adjusted hazard ratio [HR]: 2.04; 95%CI: 0.71-5.88) and a similar risk for major bleeding (HR: 1.12; 95%CI: 0.47-2.63) than those with symptomatic SVT. Active cancer was associated with at increased risk for VTE recurrences (HR: 3.06; 95%CI: 1.14-8.17) and anaemia (HR: 4.11; 95%CI: 1.45-11.6) or abnormal prothrombin time (HR: 4.10; 95%CI: 1.68-10.1) were associated with at increased risk for major bleeding.

Conclusions: The rates of recurrent SVT and major bleeding were similar between patients with incidental or symptomatic SVT. Because the severity of bleeding complications during anticoagulation may outweigh the severity of VTE

recurrences in both groups, further studies should identify those SVT patients who benefit from anticoagulant therapy.

Keywords: splanchnic vein thrombosis; recurrences; bleeding; anticoagulant therapy.

Abbreviations: SVT: splanchnic vein thrombosis; VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism.

Introduction

Thrombosis in the portal venous system, which includes the mesenteric, splenic and portal veins, is collectively termed splanchnic vein thrombosis (SVT). Acute SVT may be symptomatic, but many episodes are detected incidentally in imaging studies performed for other indications, such as staging or assessing response to therapy in patients with cancer or liver diseases [1-6]. The role of anticoagulant therapy in these patients is uncertain, given the absence of randomized trials and the increased risk for bleeding in patients who often also have liver cirrhosis or cancer. Current guidelines from the American College of Chest Physicians (ACCP) recommend anticoagulant therapy in patients with symptomatic SVT (Grade 1B) and suggest no routine anticoagulation in those with incidentally found SVT (Grade 2C) [4]**.** However, supporting evidence for these recommendations is limited by the small size of the studies. Interestingly, a recent study found the outcome in 177 patients with incidental SVT to be similar to the outcome in 420 patients with symptomatic SVT, thus suggesting that similar treatment strategies should be applied [7].

The RIETE (Registro Informatizado de Enfermedad TromboEmbólica) Registry is an ongoing, multicenter, international (Spain, Belgium, Canada, Czech Republic, Ecuador, France, Greece, Israel, Italy, Latvia, Portugal, Republic of Macedonia and Switzerland) observational registry of consecutive patients with objectively confirmed acute venous thromboembolism (VTE) (ClinicalTrials.gov identifier: NCT02832245). Data from this registry have been used to evaluate outcomes after acute VTE, such as the frequency of recurrent VTE, bleeding and mortality, and risk factors for these outcomes [8-11]. The aim of the current

study was to assess the rate and severity of symptomatic VTE recurrences and major bleeding events appearing during the course of anticoagulant therapy in patients with both symptomatic and incidentally detected SVT at baseline.

Patients and Methods

Inclusion criteria

Consecutive patients with deep vein thrombosis (DVT), pulmonary embolism (PE) or SVT confirmed by objective tests (compression ultrasonography or contrast venography for DVT; helical CT-scan, ventilation-perfusion lung scintigraphy or angiography for PE; abdominal CT-scan or ultrasonography for SVT) were enrolled in RIETE. Patients were excluded if they were currently participating in a blind therapeutic clinical trial. All patients (or their relatives) provided written or oral consent for participation in the registry, in accordance with local ethics committee requirements.

Physicians participating in the RIETE registry made all efforts to enroll consecutive patients. Data were 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 coordinating center assigned patients with a unique identification number to maintain patient confidentiality and was responsible for all data management. Data quality was regularly monitored electronically, including checks to detect inconsistencies or errors, which were resolved by contacting the local coordinators. Data quality was also monitored by periodic visits to participating hospitals by contract research organizations that compared medical records with the submitted data.

Study design

This is an observational study aimed to assess the rate and severity of symptomatic VTE recurrences and major bleeding events occurring during the course of anticoagulant therapy in patients with SVT, with or without symptoms at baseline. Symptomatic SVT was considered in patients presenting with abdominal pain (with or without nausea or vomiting) and signs of SVT on abdominal CT-scan or ultrasound. Incidental SVT was considered in patients with no abdominal symptoms, in whom imaging tests were performed for other reasons. Patients with incidental SVT were further classified into two subgroups: those with SVT detected in patients presenting with symptomatic PE or DVT, and those with SVT detected during imaging studies performed for other diseases. The study was conducted using data collected from February 2012 to March 2017. This period corresponds to the time when the information on SVT was first recorded in RIETE.

The primary outcome was the rate and severity of symptomatic, objectively proven VTE recurrences and major bleeding events appearing during the course of anticoagulant therapy. VTE recurrences included recurrent symptomatic SVT, lower or upper limb DVT and PE. Recurrent symptomatic SVT was considered in patients attending the Emergency ward because of abdominal pain (with or without nausea or vomiting) and new signs of SVT on abdominal CT-scan or ultrasound, in veins with no signs of thrombosis previously. Major bleeding was defined as any overt bleed that required a transfusion of two or more units of blood, was retroperitoneal, spinal or

intracranial, or was fatal. The severity was calculated as the mortality rate within the first 10 days after the outcomes.

Baseline variables

The following parameters were recorded when the qualifying episode of SVT was diagnosed gender, age and body weight; presence of coexisting conditions such as chronic lung disease, chronic heart failure, liver disease (distinguishing between biopsy-proven liver cirrhosis and other liver disorders), esophageal varices, gastroduodenal ulcer, recent (<30 days prior to VTE) major bleeding, active cancer and laboratory data, including whole blood counts, prothrombin time and creatinine clearance (CrCl) levels at baseline. Active cancer was defined as newly diagnosed cancer, metastatic cancer, or cancer that was being treated (i.e. surgery, chemotherapy, radiotherapy, support therapy). Anemia was considered when hemoglobin levels were <12 g/dL in women or <13 g/dL in men. CrCl levels were measured according to the Cockcroft and Gault formula [12]. The localization of SVT (isolated portal-, mesenteric-, splenic vein thrombosis, or combinations) was also considered.

Treatment and Follow-up

Patients were managed according to the clinical practice of each participating hospital (i.e., there was no standardization of treatment). The type, dose and duration of anticoagulant therapy were recorded. After SVT diagnosis, all patients were followed-up in the outpatient clinic at least during the first 3 months. The frequency of visits during follow-up was left to the decision of attending physicians. During each visit, any signs or symptoms suggesting

recurrent SVT, DVT or PE or major bleeding were noted. Most outcomes were classified as reported by the clinical centers. However, if staff at the coordinating center were uncertain how to classify a reported outcome, that event was reviewed by a central adjudicating committee (less than 10% of events).

Statistical analysis

Categorical variables were compared using the chi-square test (two-sided) and Fisher´s Exact Test (two-sided). Continuous variables were compared using Student t test. Hazard ratios (HR) and corresponding 95% confidence intervals (CI) were calculated. Incidence rates were calculated as cumulative incidence (events/100 patient-years) and compared using the hazard ratios. All analyses used time-to-event methods. Risks of recurrent VTE and major bleeding were assessed with proportional hazard Cox models. Time zero was the date of diagnosis of SVT and patients were censored at the time of discontinuation of anticoagulation, at the time of death or at the last date for which outcome data were available. We assessed the rates of symptomatic, objectively proven VTE recurrences (the composite of SVT, DVT or PE) and major bleeding in patients presenting with SVT, with or without symptoms. Crude and adjusted HRs (as well as their 95%CI) were estimated. Covariates included in the adjusted model were those for which a statistically significant difference (a threshold p-value of 0.1 was set to assess significance of differences) was found between the different variables, and a backward selection was used for the covariate selection in the multivariable model. Statistical analyses were conducted with SPSS for Windows Release (version 20, SPSS Inc. Chicago, Illinois).

Results

Up to March 2017, 521 patients with SVT were recruited in RIETE. Of these, 212 (41%) had symptomatic SVT. Among 309 patients with incidental SVT, 118 had SVT detected during admission for PE or DVT in the lower or upper limbs and 191 had no additional VTE disorders. Overall, 207 patients (40%) had isolated portal vein thrombosis, 91 (17%) had mesenteric vein thrombosis, 56 (11%) splenic vein thrombosis and 167 (32%) had thrombosis in several splanchnic veins. Among patients with incidental SVT, those without concomitant thrombosis in other sites were more likely to have liver cirrhosis, gastroduodenal ulcer, cancer, anaemia, platelet count <100,000/µL or to have only one thrombosed vein than those with symptomatic SVT (Table 1). Patients with incidental SVT and symptomatic DVT or PE were less likely men, less likely to have cirrhosis or esophageal varices and more likely to have cancer or renal insufficiency than those with symptomatic SVT.

Most patients in all three subgroups received anticoagulant therapy, both initially and for long-term (Table 2). Low-molecular-weight heparin (LMWH) was the most prescribed drug in all 3 subgroups, both initially (83%) and for long-term therapy (55%) at similar daily doses. The duration of anticoagulation was similar (median: 174 days in patients with symptomatic SVT, 136 in those with incidental SVT alone and 121 in those with DVT or PE).

During the course of anticoagulation (patients not receiving anticoagulant therapy were excluded from this analysis), 20 patients developed symptomatic

VTE recurrences (SVT recurrences 7 patients, lower-limb DVT 7, PE 7) and 26 had major bleeding (in the gastrointestinal tract 20) (Table 3). Five patients with major bleeding and no patient with VTE recurrences died within the first 10 days after the outcomes. Interestingly, there were 12 major bleeds (4 fatal) and only one VTE recurrence (lower limb DVT) during the first 30 days of therapy (Figure 1). Unexpectedly, while the rate of VTE recurrences was half the rate of major bleeding in patients with symptomatic SVT (5 vs. 10 events, respectively), these rates were similar in those with incidental SVT (15 vs. 16 events).

On multivariable analysis, patients with incidental SVT had a non-significantly higher risk for symptomatic VTE recurrences (adjusted hazard ratio [HR]: 2.04; 95%CI: 0.71-5.88) and a similar risk for major bleeding (HR: 1.12; 95%CI: 0.47-2.63) than those with symptomatic SVT. Moreover, patients with active cancer were at increased risk for VTE recurrences (HR: 3.06; 95%CI: 1.14-8.17) and those with anaemia (HR: 4.11; 95%CI: 1.45-11.6) or abnormal prothrombin time (HR: 4.10; 95%CI: 1.68-10.1) were at increased risk for major bleeding.

Discussion

In the literature, there is limited understanding on the natural history of patients with SVT during anticoagulation [13-21]. In this large cohort of patients, more than half (59%) were diagnosed incidentally, either in imaging studies performed for staging of cancer or liver disease or during work-up in patients with acute DVT and/or PE. The proportion of patients with incidental SVT in our series was higher than in previous reports because we included patients presenting with DVT and/or PE [6-7, 16-18]. Many patients in our cohort

(particularly those with incidental SVT) were at increased risk for bleeding, because of liver cirrhosis, gastroduodenal ulcer, esophageal varices, cancer, renal insufficiency, anemia or thrombocytopenia. The decision to prescribe anticoagulant therapy to patients with incidental SVT at high risk for bleeding is always challenging, but the majority of patients in our cohort did receive anticoagulation, at similar daily doses and for over 6 months in up to 50% of cases. Our data reveal that the mortality associated with major bleeding during the course of anticoagulation may outweigh the mortality associated with VTE recurrences, particularly during the first month of therapy.

During the course of anticoagulation, patients with incidental SVT had a non-significantly higher rate of symptomatic recurrences than those with symptomatic SVT and a similar rate of major bleeding. Although these differences disappeared on multivariable analysis, our findings agree with a recent study that suggested that patients with incidental SVT should receive anticoagulant therapy, as those with symptomatic SVT [7]. This is against the guidelines recommendations to routinely prescribe anticoagulation only in patients with symptomatic SVT. However, since the rate and severity of major bleeding in our cohort exceeded the rate and severity of VTE recurrences in all subgroups, our data suggest that we should be extremely cautious when prescribing anticoagulant therapy in these patients (with or without symptoms). We found patients with cancer to be at increased risk for VTE recurrences and those with anemia or abnormal prothrombin time at baseline to be at increased risk for bleeding. This might help to better identify at-risk patients. However,

randomized trials are needed to assess the most effective and safe therapy in patients with SVT.

Another interesting finding in our study was that over half of the symptomatic VTE recurrences in all three subgroups were as DVT or PE (rather than as SVT), thus suggesting that SVT, DVT and PE might be considered as part of the same disease. This should alert physicians taking care of patients with SVT, since early detection of DVT or PE signs or symptoms may influence on earlier management and lower mortality.

Our study has a number of limitations. First, RIETE is an observational registry and this may reduce the accuracy of the data. Patients were not treated with a standardized regimen; treatment varied with local practices and is likely to have been influenced by a physician's assessment of a patient's risk of bleeding. For the same reason in some cases the exact cause of death is not clear. Second, some patients may have died as a consequence of SVT, but it is often difficult to adjudicate the cause of death, particularly in patients with liver insufficiency or disseminated cancer. Third, it would be interesting to know the outcomes in the small subgroup of patients with incidental SVT who received no therapy. However, given the small sample size any difference would not be relevant. Fourth, we looked at symptomatic recurrences, but there could have been a number of asymptomatic recurrences that were missed if scans were not done in all patients. Fifth, the bleeding risk was higher in these patients but the difference may be driven by the fact that incidental patients either had a thrombosis for a longer time (leading to development of varices and portal

hypertension) or had more advanced disease or co-morbidities. Finally, we have no sufficient data to establish the role of specific laboratory tests (i.e. jnherited thrombophilia or JAK-2 mutation), because they were not available for all patients.

In conclusion, the mortality associated with major bleeding events appearing during anticoagulation may outweigh the mortality associated with SVT itself or VTE recurrences. The risk /benefit ratio of anticoagulant therapy in patients with SVT should be better evaluated in future studies.

Acknowledgements.

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 accounts for a **24,46%** of the total patients included in the RIETE Registry. We also thank the RIETE Registry Coordinating Center, S&H Medical Science Service, for their quality control data, logistic and administrative support and Prof. Salvador Ortiz, Universidad Autónoma Madrid and Silvia Galindo, both Statistical Advisors in S&H Medical Science Service for the statistical analysis of the data presented in this paper.

Conflict of interests.

WA has received speaker's honoraria from, and/or participated in scientific advisory boards for, Boehringer Ingelheim, Bayer, BMS-Pfizer, Daiichi Sankyo, ASPEN, Portola, Sanofi, Stago, and CSL Behring, and has received research support from Bayer. All other authors declare no competing interest.

References

1. Valla D. Splanchnic vein thrombosis. Semin Thromb Hemost 2015; 41: 494-502.
2. Ageno W. Managing unusual presentations of venous thromboembolism. J Thromb Thrombolysis 2015; 39: 304-310.
3. Ageno W, Beyer-Westendorf J, Garcia DA, Lazo-Langner A, McBane RD, Paciaroni M. Guidance for the management of venous thrombosis in unusual sites. J Thromb Thrombolysis 2016; 41: 129-143.
4. Kearon C, Akl EA, Comerota AJ, Prandoni P, et al. American College of Chest Physicians. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141: e419S-e494S.
5. DeLeve LD, Valla D-C, Garcia-Tsao G. Vascular disorders of the liver. Hepatology 2009; 49: 1729-1764.
6. Thatipelli MR, McBane RD, Hodge DO, Wysokinski WE. Survival and recurrence in patients with splanchnic vein thromboses. Clin Gastroenterol Hepatol 2010; 8: 200-205.
7. Riva N, Ageno W, Schulman S, Beyer-Westendorf J, Duce R, Malato A, Santoro R, Poli D, Verhamme P, Martinelli I, Kamphuisen P, Dentali F; International Registry on Splanchnic Vein Thrombosis (IRSVT) study group. Clinical history and antithrombotic treatment of incidentally detected splanchnic vein thrombosis: a multicentre, international prospective registry. Lancet Haematol. 2016; 3: e267-275.

8. Monreal M, Suárez C, Fajardo JA, Barba R, Uresandi F, Valle R, Rondón P; RIETE investigators Management of patients with acute venous thromboembolism: findings from the RIETE registry. Pathophysiol Haemost Thromb. 2003;33: 330-4.
9. Tzoran I, Brenner B, Papadakis M, Di Micco P, Monreal M. VTE Registry: What Can Be Learned from RIETE? Rambam Maimonides Med J.2014 ;5 (4):e0037.
10. Morillo R, Jiménez D, Aibar MÁ, Mastroiacovo D, Wells PS, Sampériz Á, Saraiva de Sousa M[7] Muriel A, Yusen RD, Monreal M; RIETE investigators. DVT Management and Outcome Trends, 2001 to 2014. Chest. 2016 ;150: 374-83.
11. Jiménez D, de Miguel-Díez J, Guijarro R, Trujillo-Santos J, Otero R, Barba R, Muriel A, Meyer G, Yusen RD, Monreal M; RIETE Investigators. Trends in the Management and Outcomes of Acute Pulmonary Embolism: Analysis From the RIETE Registry. J Am Coll Cardiol 2016;67:162-70.
12. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31-41.
13. Riva N, Dentali F, Donadini MP, Squizzato A, Ageno W. Risk of recurrence of unusual site venous thromboembolism. Hamostaseologie. 2013; 33: 225-231.
14. Condat B, Pessione F, Hillaire S, Denninger MH, Guillin MC, Poliquin M, Hadengue A, Erlinger S, Valla D. Current outcome of portal vein thrombosis in adults: risk and benefit of anticoagulant therapy. Gastroenterology 2001; 120: 490–497.

15. Dentali F, Ageno W, Witt D, Malato A, Clark N, Garcia D, McCool K, Siragusa S, Dyke S, Crowther M; WARPED consortium. Natural history of mesenteric venous thrombosis in patients treated with vitamin K antagonists: a multi-centre, retrospective cohort study. Thromb Haemost 2009; 102: 501–504.
16. Riva N, Ageno W, Poli D, Testa S, Rupoli S, Santoro R, Lerede T, Piana A, Carpenedo M, Nicolini A, Ferrini PM, Martini G, Mangione C, Contino L, Bonfanti C, Gresele P, Tosetto A. Recurrent Thrombotic Events after Discontinuation of Vitamin K Antagonist Treatment for Splanchnic Vein Thrombosis: A Multicenter Retrospective Cohort Study. Gastroenterol Res Pract 2015; 2015: 620217.
17. Ageno W, Riva N, Schulman S, Bang SM, Sartori MT, Grandone E, Beyer-Westendorf J, Barillari G, Di Minno MN, Dentali F; IRSVT study group. Antithrombotic treatment of splanchnic vein thrombosis: results of an international registry. Semin Thromb Hemost 2014; 40: 99-105.
18. Ageno W, Riva N, Schulman S, Beyer-Westendorf J, Bang SM, Senzolo M, Grandone E, Pasca S, Di Minno MN, Duce R, Malato A, Santoro R, Poli D, Verhamme P, Martinelli I, Kamphuisen P, Oh D, D'Amico E, Becattini C, De Stefano V, Vidili G, Vaccarino A, Nardo B, Di Nisio M, Dentali F. Long-term Clinical Outcomes of Splanchnic Vein Thrombosis: Results of an International Registry. JAMA Intern Med. 2015; 175:1474-1480.
19. Douketis J, Ageno W, Carrier M, Kearon C. Managing challenging patients with venous thromboembolism: a practical, case-based approach. Pol Arch Intern Med 2017; 127: 41-46.

20. Delgado MG, Seijo S, Yepes I, Achécar L, Catalina MV, García-Criado A, Abraldes JG, de la Peña J, Bañares R, Albillos A, Bosch J, García-Pagán JC. Efficacy and safety of anticoagulation on patients with cirrhosis and portal vein thrombosis. Clin Gastroenterol Hepatol 2012; 10: 776-783.
21. Violi F, Corazza GR, Caldwell SH, Perticone F, Gatta A, Angelico M, Farcomeni A, Masotti M, Napoleone L, Vestri A, Raparelli V, Basili S; PRO-LIVER Collaborators. Portal vein thrombosis relevance on liver cirrhosis: Italian Venous Thrombotic Events Registry. Intern Emerg Med. 2016; 11: 1059-1066.

Table 1. Clinical characteristics of 521 patients with splanchnic vein thrombosis, according to initial presentation.

	Symptomatic	Incidental	
		Alone	With DVT or PE
Patients, N	***212***	***191***	***118***
Clinical characteristics,			
Age (mean years±SD)	58±16	60±13	64±18
Gender (male)	132 (62%)	132 (69%)	59 (50%)
Body weight (mean kg±SD)	73±15	72±15	75±18
Co-morbidities,			
Liver cirrhosis	25 (12%)	40 (21%)	6 (5.1%)
Chronic liver disease (other)	18 (8.5%)	19 (9.9%)	5 (4.2%)
Esophageal varices	28 (13%)	33 (17%)	2 (1.7%)
Gastroduodenal ulcer	7 (3.3%)	16 (8.4%)	1 (0.85%)
Chronic lung disease	14 (6.6%)	18 (9.4%)	12 (10%)
Chronic heart failure	2 (0.94%)	6 (3.1%)	6 (5.1%)
Recent major bleeding	7 (3.3%)	9 (4.7%)	5 (4.2%)
Cancer	58 (27%)	123 (64%)	52 (44%)
Site of cancer,			
Colorectal	11 (19%)	42 (34%)	10 (19%)
Pancreas	13 (22%)	25 (20%)	10 (19%)
Hematologic	10 (17%)	4 (3.3%)	6 (12%)
Liver	4 (6.9%)	13 (11%)	5 (9.6%)
Biliary system	1 (1.7%)	6 (4.9%)	5 (9.6%)
Other	19 (33%)	33 (27%)	16 (31%)
Blood tests,			
Anaemia	91 (43%)	105 (55%)	55 (47%)
Platelet count <100,000/μL	23 (11%)	38 (20%)	11 (9.3%)
Abnormal prothrombin time	38 (18%)	21 (11%)	16 (14%)
CrCl levels <50 mL/min	23 (11%)	20 (10%)	26 (22%)
Site of thrombosis,			
Portal vein alone	68 (32%)	93 (49%)	46 (39%)
Mesenteric vein alone	39 (18%)	30 (16%)	22 (19%)
Splenic vein alone	8 (3.8%)	18 (9.4%)	30 (25%)
Combinations of the above	97 (46%)	50 (26%)	20 (17%)

Abbreviations: SD, standard deviation; CrCl: creatinine clearance; DVT: deep vein thrombosis; PE: pulmonary embolism.

Table 2: Treatment strategies, according to initial presentation.

	Symptomatic	Incidental	
		Alone	With DVT or PE
Patients, N	***212***	***191***	***118***
Initial therapy,			
Low-molecular-weight-heparin	183 (86%)	149 (78%)	99 (84%)
Mean LMWH doses (IU/Kg/day)	162±50	140±47	174±39
Unfractionated heparin	14 (6.6%)	3 (1.6%)	10 (8.5%)
Fondaparinux	2 (0.94%)	7 (3.7%)	3 (2.5%)
Direct oral anticoagulants	1 (0.49%)	0	3 (2.6%)
Thrombolytics	1 (0.47%)	0	1 (0.85%)
Other	2 (0.94%)	4 (2.1%)	1 (0.85%)
No anticoagulant therapy	9 (4.2%)	27 (14%)	1 (0.85%)
Vena cava filter	0	0	5 (4.2%)
Long-term therapy,			
Vitamin K antagonists	75 (35%)	33 (17%)	49 (42%)
Low-molecular-weight-heparin	119 (56%)	121 (63%)	47 (40%)
Mean LMWH doses (IU/Kg/day)	141±45	131±41	162±40
Fondaparinux	1 (0.47%)	7 (3.7%)	3 (2.5%)
Direct oral anticoagulants	4 (2.0%)	3 (1.8%)	7 (6.5%)
Other	0	2 (1.0%)	2 (1.7%)
No anticoagulant therapy	8 (3.8%)	25 (13%)	3 (2.5%)
Duration of anticoagulant therapy,			
Mean days (±SD)	364±614	270±500	282±524
Median days (IQR)	174 (102-370)	136 (94-279)	121 (79-325)
Over 6 months	99 (48%)	64 (37%)	51 (43%)
Over 12 months	53 (26%)	30 (18%)	27 (23%)

Abbreviations: SVT, splanchnic vein thrombosis; LMWH: low-molecular-weight heparin; IU: international units; SD, standard deviation; IQR: interquartile range; DVT: deep vein thrombosis; PE: pulmonary embolism.

Table 3. Clinical outcomes during the course of anticoagulant therapy.

	Symptomatic		Incidental			
			Alone		With DVT or PE	
	N	Events per 100 patient-years	N	Events per 100 patient-years	N	Events per 100 patient-years
Patients, N	***205***		***167***		***118***	
Recurrent, symptomatic SVT	2	0.99 (0.17-3.29)	4	3.24 (1.03-7.81)	1	1.10 (0.06-5.43)
Symptomatic PE	2	0.98 (0.16-3.24)	2	1.62 (0.27-5.36)	3	3.38 (0.86-9.21)
Symptomatic lower limb DVT	1	0.49 (0.02-2.43)	3	2.43 (0.62-6.60)	3	3.33 (0.85-9.05)
Any of the above	5	2.51 (0.92-5.56)	9	7.49 (3.65-13.7)*	6	6.83 (2.77-14.2)
Major bleeding	10	4.92 (2.50-8.77)	8	6.50 (3.02-12.3)	8	9.03 (4.19-17.1)
Site of major bleeding						
Gastrointestinal	9	4.43 (2.16-8.13)	7	5.68 (2.49-11.2)	4	4.47 (1.42-10.8)
Death	23	11.3 (7.31-16.6)	18	14.4 (8.79-22.3)	26	28.6 (19.1-41.3)†
Causes of death						
Disseminated cancer	14	6.86 (3.90-11.2)	13	10.4 (5.78-17.3)	14	15.4 (8.76-25.2)*
Bleeding	2	0.98 (0.16-3.24)	1	0.80 (0.04-3.94)	2	2.20 (0.37-7.26)
Liver failure	2	0.98 (0.16-3.24)	0	-	1	1.10 (0.05-5.42)
Bowel occlusion	1	0.49 (0.02-2.42)	0	-	0	-
Pulmonary embolism	0	-	0	-	1	1.10 (0.05-5.42)

Differences between incidental and symptomatic SVT: *p <0.05; †p <0.01; ‡p <0.001

Abbreviations: SVT, splanchnic vein thrombosis; PE, pulmonary embolism; DVT, deep vein thrombosis.

Table 4. Uni- and multivariable analyses for VTE recurrences and major bleeding during anticoagulation.

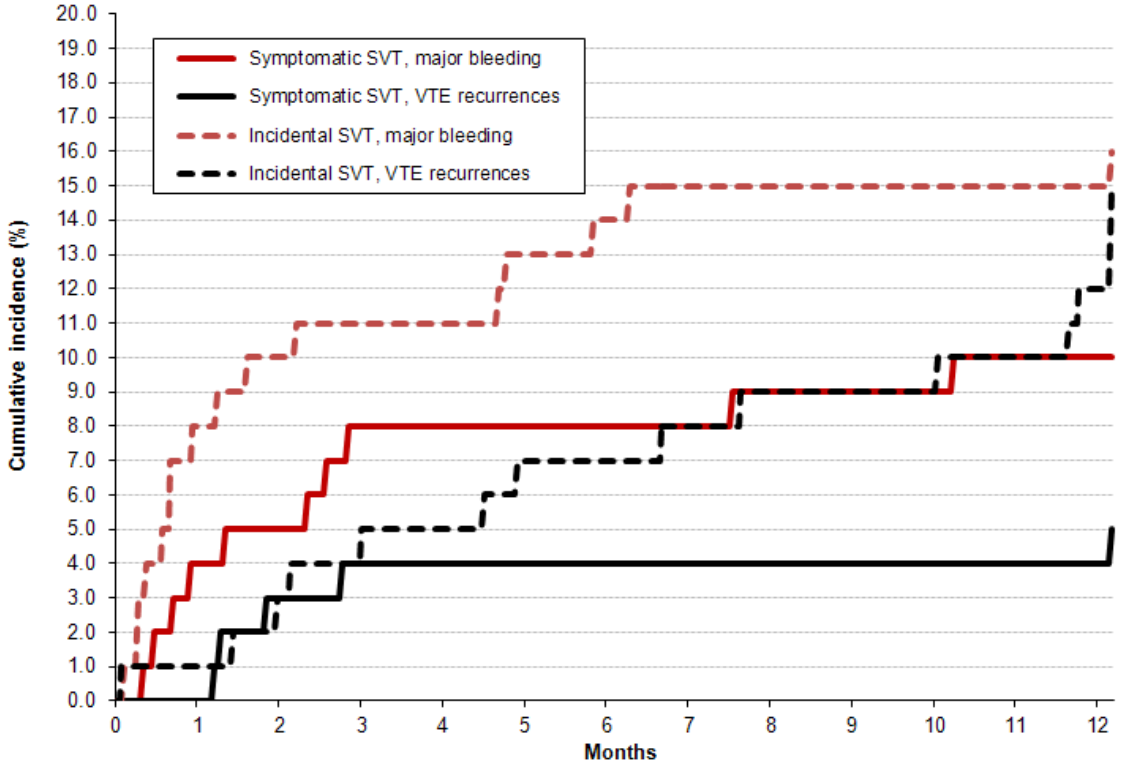
	VTE recurrences		Major bleeding	
	Crude HR (95%CI)	Adjusted HR (95%CI)	Crude HR (95%CI)	Adjusted HR (95%CI)
Outcomes, N	***20***		***26***	
Clinical characteristics,				
Age >70 years	0.36 (0.08-1.56)	0.38 (0.09-1.65)	1.99 (0.90-4.39)	2.40 (0.98-5.87)
Male gender	0.91 (0.37-2.20)	-	0.91 (0.42-1.99)	-
Body weight <70 kg	1.16 (0.47-2.84)	-	2.63 (1.19-5.79)	1.94 (0.83-4.53)
Co-morbidities,				
Liver cirrhosis	0.52 (0.07-3.91)	-	2.59 (1.04-6.49)	0.59 (0.13-2.56)
Chronic liver disease (other)	-	-	1.76 (0.53-5.88)	
Esophageal varices	-	-	3.67 (1.53-8.81)	1.65 (0.42-6.47)
Gastroduodenal ulcer	3.89 (0.89-17.1)	2.97 (0.68-13.0)	4.82 (1.65-14.1)	2.77 (0.64-12.1)
Chronic lung disease	0.73 (0.10-5.47)	-	1.66 (0.50-5.53)	-
Chronic heart failure	2.29 (0.30-17.5)	-	1.59 (0.21-11.8)	-
Recent major bleeding	-	-	4.68 (1.40-15.7)	2.59 (0.64-10.5)
Cancer	3.86 (1.48-10.1)	3.06 (1.14-8.17)	1.26 (0.58-2.72)	-
Blood tests,				
Anaemia	1.26 (0.52-3.05)	-	5.74 (2.16-15.3)	4.11 (1.45-11.6)
Platelet count <100,000/µL	-	-	3.13 (1.31-7.46)	1.65 (0.55-4.92)
Abnormal prothrombin time	-	-	5.66 (2.59-12.3)	4.10 (1.68-10.1)
CrCl levels <50 mL/min	0.50 (0.07-3.76)	-	2.06 (0.77-5.49)	0.62 (0.20-1.95)
Site of thrombosis,				
Several veins (vs. only one)	0.69 (0.26-1.81)	-	0.56 (0.22-1.39)	-
SVT symptoms,				
Incidental (vs. symptomatic)	2.56 (0.94-7.14)	2.04 (0.71-5.88)	1.23 (0.56-2.70)	1.12 (0.47-2.63)

Abbreviations: VTE, venous thromboembolism; CrCl, creatinine clearance; SVT, splanchnic vein thrombosis; HR, hazard ratio; CI, confidence intervals.

Variables included in the multivariable analysis for VTE recurrences: age, gastroduodenal ulcer, active cancer and SVT symptoms.

Variables included in the multivariable analysis for major bleeding: age, weight, liver cirrhosis, esophageal varices, gastroduodenal ulcer, recent major bleeding, active cancer, anaemia, thrombocytopenia, abnormal prothrombin time, CrCl levels and SVT symptoms.

Figure 1. Cumulative rates of VTE recurrences and major bleeding events during the course of anticoagulant therapy.



Days		*30*	*90*	*180*	*240*	*360*
Symptomatic SVT	***Patients at risk, N***	*196*	*179*	*133*	*86*	*63*
	Recurrent SVT	0	2 (1.12%)	2 (1.12%)	2 (1.12%)	2 (1.12%)
	DVT or PE	0	2 (1.11%)	2 (1.11%)	2 (1.11%)	2 (1.11%)
	Major bleeding	4 (2.06%)	8 (4.28%)	8 (4.28%)	9 (5.47%)	10 (7.02%)
Incidental STV	***Patients at risk, N***	*274*	*241*	*169*	*99*	*70*
	Recurrent SVT	0	2 (0.82%)	3 (1.28%)	5 (3.38%)	5 (3.38%)
	DVT or PE	1 (0.35%)	3 (1.22%)	5 (2.66%)	5 (2.66%)	8 (7.3%)
	Major bleeding	8 (2.93%)	11 (4.13%)	14 (6.36%)	15 (7.23%)	15 (7.23%)

Abbreviations: VTE, venous thromboembolism; SVT, splanchnic vein thrombosis; DVT, deep vein thrombosis.

Appendix

Coordinator of the RIETE Registry: Dr. Manuel Monreal (Spain)

RIETE Steering Committee Members: Dr. Hervè Decousus (France)
Dr. Paolo Prandoni (Italy)
Dr. Benjamin Brenner (Israel)

RIETE National Coordinators: Dr. Raquel Barba (Spain)
Dr. Pierpaolo Di Micco (Italy)
Dr. Laurent Bertoletti (France)
Dr. Inna Tzoran (Israel)
Dr. Abilio Reis (Portugal)
Dr. Henri Bounameaux (Switzerland)
Dr. Radovan Malý (Czech Republic)
Dr. Philip Wells (Canada)
Dr. Peter Verhamme (Belgium)
Dr. Marijan Bosevski (Republic of Macedonia)
Dr. Joseph A. Caprini (USA)

RIETE Registry Coordinating Center: S & H Medical Science Service

Members of the RIETE Group: SPAIN: Adarraga MD, Aibar MA, Alfonso M, Aranda C, Arcelus JI, Ballaz A, Barba R, Barrón M, Barrón-Andrés B, Bascuñana J, Blanco-Molina A, Braun B, Camon AM, Carrasco C, Chasco L, Cruz AJ, Cuevas G, de Miguel J, del Pozo R, del Toro J, Díaz-Pedroche MC, Díaz-Peromingo JA, Falgá C, Fernández-Aracil C, Fernández-Capitán C, Fernández-Muixi J, Fidalgo MA, Font C, Font L, Furest I, García MA, García-Bragado F, García-Morillo M, García-Raso A, García-Rodenas M, Gavín O, Gómez C, Gómez V, González J, Grau E, Guijarro R, Guirado L, Gutiérrez J, Hernández-Blasco L, Hernando E, Isern V, Jara-Palomares L, Jaras MJ, Jiménez D, Jiménez R, Joya MD, Lima J, Llamas P, Lobo JL, López-Jiménez L, López-Miguel P, López-Reyes R, López-Sáez JB, Lorente MA, Lorenzo A, Loring M, Lumbierres M, Madridano O, Maestre A, Marchena PJ, Martín M, Martín-Martos F, Monreal M, Morales MV, Nieto JA, Núñez MJ, Olivares MC, Otalora S, Otero R, Pedrajas JM, Pellejero G, Pérez-Ductor C, Peris ML, Pons I, Porras JA, Riera-Mestre A, Rivas A, Rodríguez-Dávila MA, Rosa V, Rubio CM, Ruiz-Artacho P, Sahuquillo JC, Sala-Sainz MC, Sampériz A, Sánchez-Martínez R, Sancho T, Soler S, Soto MJ, Suriñach JM, Tolosa C, Torres MI, Trujillo-Santos J, Uresandi F, Usandizaga E, Valle R, Vela J, Villalobos A, **ARGENTINA**: Vázquez FJ, Vilaseca A, **BELGIUM**: Vanassche T, Vandenbriele C, Verhamme P, **CANADA**: Wells P, **CZECH REPUBLIC**: Hirmerova J, Malý R, **ECUADOR**: Salgado E, Sánchez GT, **FRANCE**: Benzidia I, Bertoletti L, Bura-Riviere A, Falvo N, Farge-Bancel D, Hij A, Merah A, Mahé I, Moustafa F, Quere I, **ISRAEL**: Braester A, Brenner B, Ellis M, Tzoran I, **ITALY**: Antonucci G, Bilora F, Brandolin B, Bucherini E, Cattabiani C, Ciammaichella M, Dentali F, Di Micco P, Duce R, Giorgi-Pierfranceschi M, Grandone E, Imbalzano E, Lessiani G, Maggi F, Maida R, Mastroiacovo D, Niglio A, Pace F, Pesavento R, Pinelli M, Poggio R, Prandoni P, Quintavalla R, Rocci A, Siniscalchi C, Tiraferri E, Tufano A, Visonà A, Zalunardo B, **LATVIA**: Skride A, **REPUBLIC OF MACEDONIA**: Bosevski M, Zdraveska M, **SWITZERLAND**: Bounameaux H, Erdmann A, Fresa M, Mazzolai L, USA: Caprini J.

Highlights

1. Current guidelines recommend to anticoagulate SVT only if symptomatic

2. We assessed the rate and severity of VTE recurrences and major bleeding during therapy

3. During anticoagulation, the severity of bleeding may outweigh the severity of recurrences

4. Further studies should identify what SVT patients may benefit from anticoagulation