

Original Investigation

Long-term Clinical Outcomes of Splanchnic Vein Thrombosis Results of an International Registry

Walter Ageno, MD; Nicoletta Riva, MD; Sam Schulman, MD; Jan Beyer-Westendorf, MD; Soo Mee Bang, MD; Marco Senzolo, MD; Elvira Grandone, MD; Samantha Pasca, MD; Matteo Nicola Dario Di Minno, MD; Rita Duce, MD; Alessandra Malato, MD; Rita Santoro, MD; Daniela Poli, MD; Peter Verhamme, MD; Ida Martinelli, MD; Pieter Kamphuisen, MD; Doyeun Oh, MD; Elbio D'Amico, MD; Cecilia Becattini, MD; Valerio De Stefano, MD; Gianpaolo Vidili, MD; Antonella Vaccarino, MD; Barbara Nardo, MD; Marcello Di Nisio, MD; Francesco Dentali, MD

IMPORTANCE Little information is available on the long-term clinical outcome of patients with splanchnic vein thrombosis (SVT).

OBJECTIVE To assess the incidence rates of bleeding, thrombotic events, and mortality in a large international cohort of patients with SVT.

DESIGN, SETTING, AND PARTICIPANTS A prospective cohort study was conducted beginning May 2, 2008, and completed January 30, 2014, at hospital-based centers specialized in the management of thromboembolic disorders; a 2-year follow-up period was completed January 30, 2014, and data analysis was conducted from July 1, 2014, to February 28, 2015. Participants included 604 consecutive patients with objectively diagnosed SVT; there were no exclusion criteria. Information was gathered on baseline characteristics, risk factors, and antithrombotic treatment. Clinical outcomes during the follow-up period were documented and reviewed by a central adjudication committee.

MAIN OUTCOMES AND MEASURES Major bleeding, defined according to the International Society on Thrombosis and Hemostasis; bleeding requiring hospitalization; thrombotic events, including venous and arterial thrombosis; and all-cause mortality.

RESULTS Of the 604 patients (median age, 54 years; 62.6% males), 21 (3.5%) did not complete follow-up. The most common risk factors for SVT were liver cirrhosis (167 of 600 patients [27.8%]) and solid cancer (136 of 600 [22.7%]); the most common sites of thrombosis were the portal vein (465 of 604 [77.0%]) and the mesenteric veins (266 of 604 [44.0%]). Anticoagulation was administered to 465 patients in the entire cohort (77.0%) with a mean duration of 13.9 months; 175 of the anticoagulant group (37.6%) received parenteral treatment only, and 290 patients (62.4%) were receiving vitamin K antagonists. The incidence rates (reported with 95% CIs) were 3.8 per 100 patient-years (2.7-5.2) for major bleeding, 7.3 per 100 patient-years (5.8-9.3) for thrombotic events, and 10.3 per 100 patient-years (8.5-12.5) for all-cause mortality. During anticoagulant treatment, these rates were 3.9 per 100 patient-years (2.6-6.0) for major bleeding and 5.6 per 100 patient-years (3.9-8.0) for thrombotic events. After treatment discontinuation, rates were 1.0 per 100 patient-years (0.3-4.2) and 10.5 per 100 patient-years (6.8-16.3), respectively. The highest rates of major bleeding and thrombotic events during the whole study period were observed in patients with cirrhosis (10.0 per 100 patient-years [6.6-15.1] and 11.3 per 100 patient-years [7.7-16.8], respectively); the lowest rates were in patients with SVT secondary to transient risk factors (0.5 per 100 patient-years [0.1-3.7] and 3.2 per 100 patient-years [1.4-7.0], respectively).

CONCLUSIONS AND RELEVANCE Most patients with SVT have a substantial long-term risk of thrombotic events. In patients with cirrhosis, this risk must be balanced against a similarly high risk of major bleeding. Anticoagulant treatment appears to be safe and effective in most patients with SVT.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Walter Ageno, MD, Department of Clinical and Experimental Medicine, University of Insubria, Viale Borri 57, 21100, Varese, Italy (agewal@yahoo.com).

Splanchnic vein thrombosis (SVT) is an uncommon but potentially life-threatening disease. It can affect the portal vein, the mesenteric veins, the splenic vein, or the suprahepatic veins in the Budd-Chiari syndrome, and the involvement of 2 or more different abdominal vein segments is not rare.¹⁻³ The clinical presentation of SVT can vary from cases with acute abdomen or active gastrointestinal bleeding to a proportion (approximately 20%-30%) of cases that are detected incidentally.^{1,2,4} The heterogeneity of the population is the result of different underlying clinical conditions including liver cirrhosis; solid cancer; Philadelphia-negative myeloproliferative neoplasms and the *JAK2V617F* (OMIM 147796.0001) mutation; intra-abdominal inflammatory conditions, such as pancreatitis, inflammatory bowel disease, and diverticulitis; and surgery.²⁻⁴

The site and extent of SVT, as well as the identification of underlying provoking factors, are crucial to define the prognosis and drive appropriate management strategies. Anticoagulants represent the mainstay of treatment for SVT, but their use is often limited by the concomitant presence of risk factors for bleeding.^{2,4} Indeed, the long-term clinical outcome of SVT is poorly defined, and there is scant information on the risks and benefits of antithrombotic treatment in this population. Studies^{2,5-7} suggest that anticoagulants may effectively reduce the risk of recurrence and improve recanalization, but bleeding rates are often reported to exceed the risk of recurrence. However, most studies have focused on very select and often small populations or had a retrospective design. In addition, information on bleeding rates is hampered by the lack of a standardized definition of major bleeding in this setting. The aim of the present study was to assess the long-term rates of clinical outcomes during a 2-year follow-up in a large prospective cohort of patients with SVT.

Methods

Study Design

This was a multicenter, international, prospective cohort study promoted through the International Society on Thrombosis and Hemostasis (ISTH). Centers affiliated with this society worldwide were invited to participate. Between May 2, 2008, and January 30, 2012, investigators enrolled consecutive patients with objectively diagnosed SVT within no more than 6 months prior to their inclusion in the trial. There were no exclusion criteria. The protocol was approved by the institutional review board or ethics committee of each participating center, and written informed consent was obtained from all patients where requested (in some countries, informed consent is not requested for observational studies); participants did not receive financial compensation. Data were collected, maintained, and analyzed by the Research Center on Thromboembolic Diseases and Antithrombotic Drugs of the University of Insubria, Varese, Italy.

The diagnosis of SVT was accepted if confirmed by Doppler ultrasonography, computed tomography, magnetic resonance imaging, or angiography or during laparoscopic or abdominal surgery. Treatment decisions were entirely at the discretion of attending clinicians, and no therapeutic algorithms were pro-

vided. Patients were monitored with regular visits for 2 years, and all participating centers were invited to provide follow-up information on study outcomes at least every 6 months. Follow-up was completed January 30, 2014, and our statistical analysis was conducted from July 1, 2014, to February 28, 2015.

Investigators recorded data on a computer-based case report form and submitted the forms to a centralized coordinating center through a secure website. The study coordinating center at the University of Insubria used multiple data quality-control procedures to optimize data quality. Data were regularly monitored to detect inconsistencies or errors, and queries requiring resolution by the local investigators were sent to each site. All reported clinical outcomes were adjudicated by a central adjudication committee.

Study Variables

The following baseline data were collected at the time of patients' inclusion in the study: demographic characteristics, family or personal history of venous thromboembolism, presence of inherited and acquired thrombophilic risk factors and markers of Philadelphia-negative myeloproliferative neoplasms, use of hormone therapy and presence of other potential risk factors (eg, cancer, intra-abdominal inflammatory conditions, hematologic disorders, recent abdominal surgery, liver cirrhosis), clinical characteristics at the time of presentation and at the time of diagnosis, alterations of routine blood test results performed at the time of diagnosis, results of performed imaging tests, results of other diagnostic/therapeutic techniques, use of unfractionated heparin or low-molecular-weight heparin, use of vitamin K antagonists, and use of other antithrombotic and/or thrombolytic drugs or any other therapeutic intervention performed for the purpose of the treatment of SVT. Detailed information on the baseline characteristics and strategies used for the initial treatment have been published.⁴

During follow-up, information on the duration of antithrombotic treatment and on clinical outcomes (major bleeding, vascular events, mortality) was collected. *Major bleeding* was defined as fatal bleeding, bleeding leading to surgery, bleeding occurring in a critical organ (intracranial or intraspinal, retroperitoneal, intraocular resulting in visual impairment), overt bleeding associated with a drop in hemoglobin levels of 2 g/dL or more (to convert to grams per liter, multiply by 10), bleeding requiring the transfusion of 2 U or more of red blood cells, or bleeding leading to hospitalization. Thrombotic events included *recurrent SVT*, defined as thrombus extension or occurrence in a previously patent segment, symptomatic venous thromboembolism in other sites as diagnosed by appropriate imaging tests according to the site of thrombosis, arterial thrombosis (acute coronary syndromes, acute ischemic stroke, transient ischemic attack, acute peripheral arterial disease) diagnosed according to standard criteria, and mesenteric infarction as evidenced by a pathology specimen.

Statistical Analysis

Baseline characteristics of the enrolled population are reported as descriptive statistics; continuous variables are expressed as mean (SD) or as median (interquartile range) when

Table 1. Baseline Characteristics of the Study Cohort

Characteristic	Patients With SVT, No./Total No. (%) (n = 604)
Age, median (IQR), y	54 (43-64)
Male sex	378/604 (62.6)
Asian ethnicity	137/604 (22.7)
Personal history of VTE	68/598 (11.4)
Family history of VTE	50/595 (8.4)
Clinical presentation	
Incidentally detected	177/597 (29.7)
Abdominal pain	329/597 (55.1)
GI tract bleeding (including hematemesis, hematochezia, melena)	52/597 (8.7)
Ascites or increased abdominal girth	62/597 (10.4)
Involved veins	
Multiple veins	232/604 (38.4)
Portal vein thrombosis	465/604 (77.0)
Mesenteric vein thrombosis	266/604 (44.0)
Suprahepatic vein thrombosis	55/604 (9.1)
Splenic vein thrombosis	138/604 (22.9)
Risk factors	
Unprovoked	163/600 (27.2)
Hepatic cirrhosis	167/600 (27.8)
Solid cancer	136/600 (22.7)
Myeloproliferative neoplasm	49/600 (8.2)
Inflammatory bowel disease	11/600 (1.8)
Other intra-abdominal inflammations or infections	60/600 (10.0)
Abdominal surgery	54/600 (9.0)
Hormonal therapy	25/226 (11.1)
Pregnancy or puerperium	8/226 (3.53)
Genetic mutations, No./No. tested (total %)	
JAK2V617F mutation	40/199 (20.1)
Prothrombin G20210A mutation	33/286 (11.5)
Factor V Leiden mutation	37/331 (11.2)
Laboratory test results	
Hemoglobin ≤ 10 g/dL	127/480 (26.5)
Platelets $\leq 100 \times 10^3/\text{mm}^3$	133/483 (27.5)

Abbreviations: GI, gastrointestinal; IQR, Interquartile range; SVT, splanchnic vein thrombosis; VTE, venous thromboembolism.

SI conversion factors: To convert hemoglobin concentration to grams per liter, multiply by 10; platelets to $\times 10^9/\text{L}$, multiply by 1.

data did not have a normal distribution (according to the Wilk-Shapiro test); categorical data are given as counts and percentages. The primary analysis was performed up to the first adjudicated major bleeding or thrombotic event. The number of events is expressed as incidence rate, which was calculated as the number of events per 100 patient-years of observation with 95% CI. Overall survival rates were assessed by the Kaplan-Meier method and compared between patients with liver cirrhosis and patients with nonmalignant, noncirrhotic SVT using the log-rank test. Furthermore, we calculated the incidence rate of major bleeding and thrombotic events during anticoagulant treatment and after treatment discontinuation (on-treatment and off-treatment analysis).

To explore the role of potential predictors of major bleeding and thrombotic events, different multivariable Cox proportional hazards regression model analyses were performed, using backward stepwise elimination (with levels of $P < .05$ for inclusion and $P > .10$ for exclusion) and stratifying by center, to account for possible heterogeneity of within-center bleeding and thrombotic risk. We started analysis with the following variables: age, male sex, Asian ethnicity, personal history of venous thromboembolism, incidentally detected SVT, gastrointestinal bleeding at onset, ascites at onset, suprahepatic vein thrombosis, unprovoked SVT, solid cancer, liver cirrhosis, overt myeloproliferative neoplasm, recent abdominal surgery, inflammatory bowel disease, anemia (hemoglobin concentration ≤ 10 g/dL), thrombocytopenia (platelet level $\leq 100 \times 10^3/\mu\text{L}$ [to convert to $\times 10^9/\text{L}$, multiply by 1]), and anticoagulant treatment (considered a time-dependent variable). Multivariable analysis was then repeated in patients without liver cirrhosis and in those with liver cirrhosis. Variables with a significance level of $P < .05$ in multivariable analysis were considered to be associated with the outcome of interest.

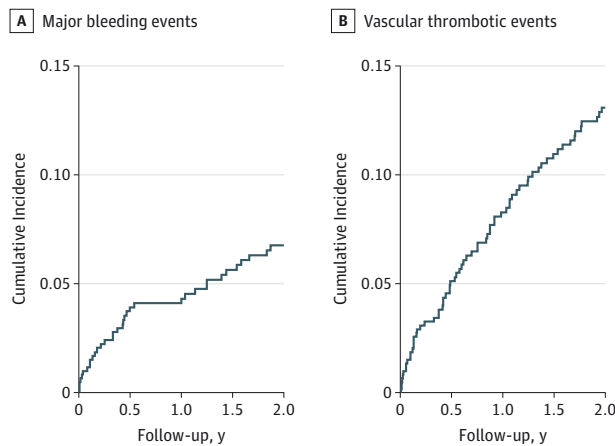
Given the paucity of prospective studies on SVT, we planned a pilot sample of 500 patients, including all sites of thrombosis. Because we expected a possible dropout rate of 10%, we planned to enroll a minimum of 550 patients. Stata SE, version 12 (StataCorp LP), was used for statistical management of the data.

Results

A total of 604 patients from 31 centers in 11 countries were enrolled in this prospective study. The list of participating centers is provided in the eAppendix in the Supplement. The sample used in the present study differs from the original baseline cohort of 613 patients described elsewhere⁴ because 2 centers decided not to participate in the long-term follow-up part of the study. The baseline characteristics of the study cohort are reported in Table 1.

During the acute phase of the study, anticoagulant treatment was administered to 465 patients (77.0%), of whom 175 (37.6%) received parenteral treatment only (in most cases low-molecular-weight heparin) and 290 (62.4%) began therapy with vitamin K antagonists (267 after an initial course of parenteral treatment, 23 without parenteral treatment because SVT was diagnosed as “chronic”). Factors associated with therapeutic decisions have been previously described.⁴ Three patients (0.5%) received aspirin monotherapy.

The total duration of follow-up was 932.2 patient-years, with a median duration of 2 years (interquartile range, 1-2 years). Twenty-one patients (3.5%) did not complete the follow-up. The mean (SD) duration of anticoagulant treatment was 13.9 (9.2) months. This duration was shorter in patients who received parenteral treatment only throughout the observation period (8.2 [7.7] months) than in patients who began receiving vitamin K antagonists (16.7 [8.5] months).

Figure 1. Cumulative Incidence of Major Bleeding and Thrombotic Events in the Entire Cohort of Patients With Splanchnic Vein Thrombosis

Major Bleeding Events

There were 35 major bleeding events in the entire cohort during follow-up for an incidence rate of 3.8 per 100 patient-years (95% CI, 2.7-5.2). The cumulative incidence of major bleeding events is reported in **Figure 1A**.

In the subgroup of 465 patients receiving anticoagulant therapy, the incidence rate of major bleeding events was 3.9 per 100 patient-years (95% CI, 2.6-6.0) during anticoagulant treatment. In those who stopped treatment before the end of follow-up (39.8%), the incidence of major bleeding after treatment discontinuation was 1.0 per 100 patient-years (95% CI, 0.3-4.2). In the subgroup of never-treated patients, the incidence of major bleeding was 5.8 per 100 patient-years (95% CI, 3.1-10.7).

The site and characteristics of bleeding events are reported in **Table 2**. The case fatality rate of major bleeding events was 5.7% (95% CI, 1.0%-20.5%). However, the 2 deaths were due to bleeding from esophageal varices in patients with liver cirrhosis, neither of whom received any antithrombotic therapy. Thus, the case fatality rate of major bleeding events during anticoagulant treatment was 0% (95% CI, 0%-18.5%).

The incidence of major bleeding events was highest in patients with liver cirrhosis and lowest in patients with SVT secondary to transient risk factors (**Table 3**). **Figure 2A** shows the Kaplan-Meier curves for the cumulative incidence of major bleeding events in patients with liver cirrhosis and in patients with nonmalignant, noncirrhotic SVT (log-rank test, $P < .001$). Kaplan-Meier curves for the cumulative incidence of major bleeding events in patients with solid cancer and hematologic cancer are presented in eFigure, A in the **Supplement**.

Thrombotic Events

There were 68 thrombotic events in the entire cohort during follow-up for an incidence of 7.3 per 100 patient-years (95% CI, 5.8-9.3). Most thrombotic events (54 [79.4%]) occurred in the venous system: 41 (75.9%) as recurrent SVT and 13 (24.1%) as venous thromboembolism in other sites. The sites of throm-

Table 2. Major Bleeding Events

Characteristic	No. (%)
Major bleeding events ^a	35
Incidence rate of bleeding (95% CI), per 100 patient-years	3.8 (2.7-5.2)
Site of bleeding	
Gastrointestinal tract	28 (80.0)
Hemoperitoneum from rupture of hepatocellular carcinoma	1 (2.9)
Intracranial/intraspinal	2 (5.7)/1 (2.9)
Intraocular	1 (2.9)
Genital tract	2 (5.7)
Severity of bleeding	
Fatal	2 (5.7)
Critical organ	4 (11.4)
Hb concentration reduction ≥ 2 g/dL or RBC transfusion ≥ 2 U	22 (62.9)
Requiring hospitalization as only criteria	7 (20.0)

Abbreviations: Hb, hemoglobin; RBC, red blood cell.

SI conversion factor: To convert Hb concentration to grams per liter, multiply by 10.

^a Fourteen major bleeding events occurred during vitamin K antagonist treatment: the international normalized ratio was above the therapeutic range in 5 patients, within the therapeutic range in 5 patients, and not available in 4 patients.

botic events are available in eTable 1 in the **Supplement**. The cumulative incidence of thrombotic events is shown in **Figure 1B**.

In the subgroup of 465 patients receiving anticoagulant therapy, the incidence of thrombotic events was 5.6 per 100 patient-years (95% CI, 3.9-8.0) during anticoagulant treatment and 10.5 per 100 patient-years (95% CI, 6.8-16.3) after treatment discontinuation. In the subgroup of patients who remained untreated, the incidence of thrombotic events was 9.2 per 100 patient-years (95% CI, 5.7-15.1).

The case fatality rate of thrombotic events was 13.2% (95% CI, 6.60%-24.15%). Of the 9 fatal thrombotic events, 5 were intestinal infarctions occurring early after SVT (mean time elapsed, 0.7 months). Three of these patients were receiving low-molecular-weight heparin. One additional fatal intestinal infarction occurred 15 months after the index event in a patient with myeloproliferative neoplasm who was not receiving anticoagulant treatment. The other fatal thrombotic events included 2 episodes of sudden death in patients with cancer in whom pulmonary embolism (PE) could not be ruled out, with neither of these patients receiving treatment, and 1 fatal PE in a patient with cancer receiving low-molecular-weight heparin.

Patients with liver cirrhosis had the highest incidence of thrombotic events, and patients with SVT secondary to transient risk factors had the lowest rates (**Table 3**). **Figure 2B** shows the Kaplan-Meier curves for the cumulative incidence of thrombotic events in patients with liver cirrhosis and in patients with nonmalignant, noncirrhotic SVT (log-rank test, $P = .01$). Kaplan-Meier curves for the cumulative incidence of thrombotic events in patients with solid cancer and hematologic cancer are available in eFigure, B in the **Supplement**. The incidence of thrombotic outcomes was similar between patients with symptomatic SVT and patients with incidentally detected SVT.

Table 3. Incidence of Outcome Events in Subgroups With Different Risk Factors^a

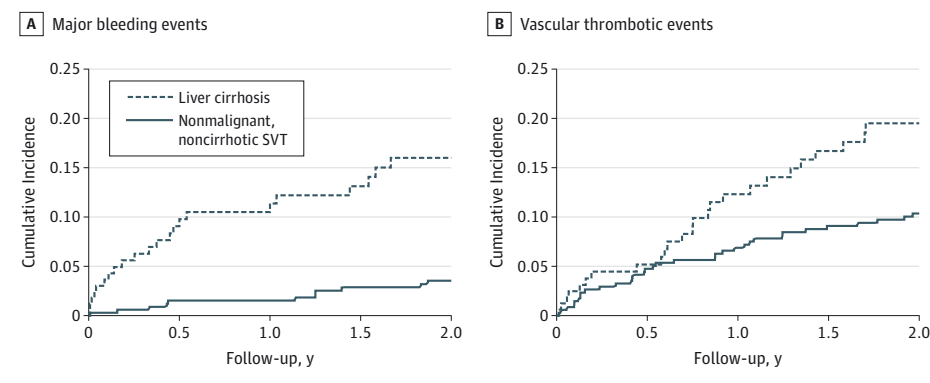
Outcome	Liver Cirrhosis (n = 167)	Solid Cancer (n = 136)	Myeloproliferative Neoplasm (n = 49)	Unprovoked SVT (n = 163)	Transient Risk Factors ^b (n = 105)
Major bleeding events	22 Events; 10.0 per 100 patient-years (6.6-15.1)	7 Events; 4.4 per 100 patient-years (2.1-9.3)	3 Events; 3.6 per 100 patient-years (1.1-11.1)	5 Events; 1.7 per 100 patient-years (0.7-4.2)	1 Event; 0.5 per 100 patient-year (0.1-3.7)
Thrombotic events	25 Events; 11.3 per 100 patient-years (7.7-16.8)	12 Events; 7.6 per 100 patient-years (4.3-13.3)	5 Events; 5.9 per 100 patient-year (2.5-14.3)	18 Events; 6.3 per 100 patient-year (4.0-10.0)	6 Events; 3.2 per 100 patient-year (1.4-7.0)
Mortality	45 Events; 16.8 per 100 patient-year (12.5-22.4)	67 Events; 39.5 per 100 patient-years (31.1-50.1)	3 Events; 3.4 per 100 patient-year (1.1-10.4)	7 Events; 2.3 per 100 patient-years (1.1-4.8)	5 Events; 2.5 per 100 patient-years (1.1-6.1)

Abbreviation: SVT, splanchnic vein thrombosis.

^a Some patients had more than 1 risk factor.

^b Transient risk factors included recent surgery, intra-abdominal infection, use of hormone therapy, pregnancy/puerperium, and abdominal trauma.

Figure 2. Cumulative Incidence of Major Bleeding and Thrombotic Events in Patients With Liver Cirrhosis and Nonmalignant, Noncirrhotic Splanchnic Vein Thrombosis (SVT)



Total Mortality

There were 106 deaths during follow-up for an incidence rate of 10.3 per 100 patient-years (95% CI, 8.5-12.5). Most deaths were related to underlying disorders. The incidence of total mortality in the subgroups with different risk factors is reported in Table 3.

Predictors of Bleeding and Thrombotic Outcomes

The first multivariable analysis was conducted on the whole study cohort. The presence of liver cirrhosis with and without ascites at baseline was associated with an increased risk of major bleeding, and anticoagulant treatment duration was associated with a lower hemorrhagic risk. Male sex and age were associated with an increased risk of vascular events, and anticoagulant treatment duration was associated with a lower thrombotic risk (eTable 2 and eTable 3 in the Supplement).

We subsequently repeated the multivariable analysis in subgroups of patients with and without liver cirrhosis. In patients with liver cirrhosis, anticoagulant treatment duration was independently associated with a lower risk of both major bleeding and vascular events. The association between male sex and the risk of vascular events was of borderline statistical significance (eTables 2 and 3 in the Supplement).

In patients without liver cirrhosis, none of the included variables was independently associated with major bleeding,

whereas male sex, solid cancer, myeloproliferative neoplasms, and unprovoked SVT were associated with an increased risk of vascular events during follow-up (eTables 2 and 3 in the Supplement). Anticoagulant treatment duration was independently associated with a reduced risk of thrombotic events. The results of tests of interactions between cirrhosis and other predictors are reported in eTable 4 and eTable 5 in the Supplement.

Discussion

The results of this large, prospective cohort study provide information on the long-term clinical outcomes of SVT and describe current therapeutic strategies for the secondary prevention of the disease in real-world clinical practice. Our data suggest that the risk of thrombotic events, mainly recurrent SVT or venous thrombosis in other sites, is substantial and nearly doubles the risk of major bleeding events. In addition, case fatality rates of vascular thrombotic events more than doubled the case fatality rates of hemorrhage.

As expected, the magnitude of the risks is greatly influenced by the underlying clinical conditions. In the presence of liver cirrhosis, the annual rates of thrombotic events exceeded 10%, with a similar risk of major bleeding events. Con-

versely, in patients with transient risk factors for SVT, the annualized rates of both thrombotic and bleeding events remained low. The risk of thrombotic events was substantial in patients with solid cancer, myeloproliferative neoplasms, and unprovoked SVT.

Current guidelines^{8,9} recommend anticoagulation treatment for all patients with SVT to be administered for at least 3 months and to be extended beyond this period in patients with permanent prothrombotic conditions and an acceptably low risk of bleeding. These recommendations are based on the results of few observational studies^{2,5,6} in patients with SVT but mostly rely on the evidence from studies^{10,11} on patients with lower limb deep vein thrombosis (DVT) or PE.

The results of previous studies^{2,5,6} on patients with SVT have reported more bleeding events than recurrences. In these studies, apparently only between one-third and one-half of patients received anticoagulation treatment. In the present study, most patients (77.0%) received some form of anticoagulant treatment, suggesting a possible trend toward more use of anticoagulants over the years. As reported in a previous article,⁴ factors associated with no treatment in our cohort included incidental diagnosis of SVT, gastrointestinal bleeding at onset, solid cancer, liver cirrhosis, thrombocytopenia, and the involvement of a single vein segment.

By using, for what we believe to be the first time, a modified version of the ISTH definition of major bleeding,¹² we wanted to attempt some comparisons with bleeding rates observed in studies carried out in patients with DVT of the lower limbs or PE. In a large, prospective observational study¹⁰ of patients with DVT or PE, the annualized rate of ISTH-defined major bleeding was 2.6%. This rate is similar to that observed in the present study if we exclude bleeding leading to hospitalization (not included in the standard ISTH definition), which accounted for 20% all major bleeding events.

In patients with DVT or PE, decisions on the duration of secondary prevention are based on the balance between these bleeding rates and estimated annualized recurrence rates of 3.3% after venous thrombosis secondary to transient risk factors and 7.4% after unprovoked events.¹¹ Because these rates are also comparable to those found in the present study in similar subgroups, we can speculate that, in most SVT patient subgroups, secondary prevention strategies should be the same as for patients with DVT or PE.

With regard to patients with cancer, we found the incidence of major bleeding to be at least 2 times higher than the incidence in patients without cirrhosis or cancer. Previous studies¹³ in patients with DVT or PE reported a risk of major bleeding that was twice as high in patients with cancer compared with patients without cancer. The rates of thrombotic and bleeding events in our study were only slightly higher in patients with solid cancer than in patients with a myeloproliferative neoplasm. Thus, patients with a myeloproliferative neoplasm should be considered as having a risk of outcome events during follow-up that is similar

to the risk in patients with solid cancer. For this reason, the therapeutic management for these diseases should also be similar, at least in terms of treatment duration.

With regard to patients with liver cirrhosis, we observed that most of the documented bleeding events occurred in the absence of anticoagulation therapy (including the 2 fatal events that occurred in untreated high-risk patients with liver cirrhosis and esophageal varices), and the results of the multivariable analysis suggested a benefit from anticoagulant treatment in these patients. Although it is highly likely that patients receiving anticoagulation therapy represented a population at lower risk, we did not find higher rates of hemorrhage between those who received anticoagulants compared with those who did not, and the case fatality rate for major bleeding events in patients receiving anticoagulation treatment was 0%. This finding supports the importance of considering all patients with liver cirrhosis for anticoagulant treatment in the absence of absolute contraindications.

This study has several potential limitations. The first of these is that the observational design may hamper the accuracy of data collection, including information on risk factors and outcome events. Because no diagnostic algorithm was provided, not all patients underwent a systematic search for major provoking factors for thrombosis and for bleeding; for this reason, the prevalence of such factors may be underestimated. Similarly, we cannot exclude an underreporting of outcome events. However, all participating centers act as local or national referral centers for unusual site thrombosis and are highly experienced in conducting research studies. To reduce these potential limitations associated with observational design, the study coordinating center regularly monitored all data reported in the electronic case report form and sent queries requiring resolution by the local investigators. Furthermore, to improve the accuracy of reported events, all clinical outcomes were adjudicated by a central adjudication committee. The comparatively high rates of both bleeding and cardiovascular events indicate that these measures effectively reduced the potential risk of underreporting. Second, because this study was mainly aimed to assess the incidence of major clinical outcomes, several additional, potentially relevant outcomes, such as vessel recanalization, were not routinely collected and are, therefore, insufficiently available for the analysis.

Third, although this study was intended to provide a comprehensive picture of the real-life management of SVT and describe the long-term outcome of a broad population of patients with SVT, we cannot exclude the possibility that selection bias occurred at the time of patient enrollment. For this reason, the results of this study may not be generalizable to all patients with SVT. However, we believe this study represents the largest prospective cohort of patients with SVT monitored for a sufficiently long period of time. Finally, the observation of a favorable effect of anticoagulant treatment in all patient subgroups must be considered as hypothesis generating only because the design of this study does not allow any conclusion on the efficacy and safety of a treatment.

Conclusions

Patients with SVT have a substantial long-term risk of vascular thrombotic events. In patients without cirrhosis, independent predictors of recurrence include myeloproliferative neoplasms, solid cancer, unprovoked SVT, and male sex. In these patients, the risk of major bleeding appears to be similar to the risk reported in patients with DVT or PE. In patients with liver cirrhosis and SVT, the risk of thrombotic and major

bleeding events is much higher than in other patient subgroups. An increased duration of anticoagulant treatment is associated with a significant reduction of both outcomes. Observations from the present study may help clinicians to balance the benefits and risks of anticoagulant treatment in this setting and substantially support the safety and efficacy of anticoagulant therapy in most patients with SVT. Our results thus strengthen the recommendations of the guidelines^{8,9} and provide some solid background information for the design of future trials.

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Author Affiliations: Department of Clinical and Experimental Medicine, University of Insubria, Varese, Italy (Ageno, Riva, Dentali); Department of Medicine, McMaster University, Hamilton, Ontario, Canada (Schulman); Center for Vascular Medicine and Department of Medicine III, Division of Angiology, University Hospital "Carl Gustav Carus," Dresden, Germany (Beyer-Westendorf); Department of Internal Medicine, Seoul National University, Seoul, South Korea (Bang); Multivisceral Transplant Unit, Gastroenterology, University Hospital of Padova, Padova, Italy (Senzolo); Istituto di Ricovero e Cura a Carattere Scientifico, Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy (Grandone); Center for Hemorrhagic and Thrombotic Diseases, University Hospital, Udine, Italy (Pasca); Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy (Di Minno); Unit of Cell and Molecular Biology in Cardiovascular Diseases, Centro Cardiologico Monzino, Milan, Italy (Di Minno); Thrombosis Center, Galliera Hospital, Genoa, Italy (Duce); Department of Hematology, Policlinico Universitario di Palermo, Palermo, Italy (Malato); Haemophilia Center, Azienda Ospedaliera Pugliese-Ciaccio, Catanzaro, Italy (Santoro); Thrombosis Center, Careggi Hospital, Florence, Italy (Poli); Vascular Medicine and Haemostasis, University of Leuven, Leuven, Belgium (Verhamme); A. Bianchi Bonomi Hemophilia and Thrombosis Center, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico, Ca' Granda-Ospedale Maggiore Policlinico, Milan, Italy (Martinelli); Department of Vascular Medicine, University of Groningen, Groningen, the Netherlands (Kamphuisen); Department of Internal Medicine, Pochon CHA University, Seoul, Korea (Oh); Hospital das Clínicas da Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil (D'Amico); Department of Internal and Vascular Medicine, University of Perugia, Ospedale S. Maria della Misericordia, Perugia, Italy (Becattini); Institute of Hematology, Catholic University, Rome, Italy (De Stefano); Department of Clinical Medicine, University Hospital of Sassari, Sassari, Italy (Vidili); Unità Operativa Semplice Dipartimentale di Ematologia e Malattie Trombotiche, Ospedale San Giovanni Bosco, Torino, Italy (Vaccarino); Department of Medicine I, Busto Arsizio Hospital, Busto Arsizio, Italy (Nardo); Department of Medical, Oral, and Biotechnological Sciences, University G. D'Annunzio, Chieti, Italy (Di Nisio).

Author Contributions: Drs Ageno and Riva had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Ageno, Riva, Schulman, Dentali.

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Drafting of the manuscript: Ageno, Riva, Schulman, Beyer-Westendorf, Dentali.

Critical revision of the manuscript for important intellectual content: Bang, Senzolo, Grandone, Pasca, Di Minno, Duce, Malato, Santoro, Poli, Verhamme, Martinelli, Kamphuisen, Oh, D'Amico, Becattini, De Stefano, Vidili, Vaccarino, Nardo, Di Nisio.

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REFERENCES

1. Ageno W, Dentali F, Squizzato A. How I treat splanchnic vein thrombosis. *Blood*. 2014;124(25):3685-3691.
2. Thatipelli MR, McBane RD, Hodge DO, Wysokinski WE. Survival and recurrence in patients with splanchnic vein thromboses. *Clin Gastroenterol Hepatol*. 2010;8(2):200-205.
3. Darwish Murad S, Plessier A, Hernandez-Guerra M, et al; EN-Vie (European Network for Vascular Disorders of the Liver). Etiology, management, and outcome of the Budd-Chiari syndrome. *Ann Intern Med*. 2009;151(3):167-175.
4. Ageno W, Riva N, Schulman S, et al; IRSVT Study Group. Antithrombotic treatment of splanchnic vein thrombosis: results of an international registry. *Semin Thromb Hemost*. 2014;40(1):99-105.
5. Condat B, Pessione F, Hillaire S, et al. Current outcome of portal vein thrombosis in adults: risk and benefit of anticoagulant therapy. *Gastroenterology*. 2001;120(2):490-497.
6. Spaander MCW, Hoekstra J, Hansen BE, Van Buuren HR, Leebeek FW, Janssen HLA. Anticoagulant therapy in patients with non-cirrhotic portal vein thrombosis: effect on new thrombotic events and gastrointestinal bleeding. *J Thromb Haemost*. 2013;11(3):452-459.
7. Plessier A, Darwish-Murad S, Hernandez-Guerra M, et al; European Network for Vascular Disorders of the Liver (EN-Vie). Acute portal vein thrombosis unrelated to cirrhosis: a prospective multicenter follow-up study. *Hepatology*. 2010;51(1):210-218.
8. DeLeve LD, Valla DC, Garcia-Tsao G; American Association for the Study of Liver Diseases. Vascular disorders of the liver. *Hepatology*. 2009;49(5):1729-1764.
9. Kearon C, Akl EA, Comerota AJ, 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. doi:10.1378/chest.11-2301.
10. Lecumberri R, Alfonso A, Jiménez D, et al; RIETE investigators. Dynamics of case-fatality rates of recurrent thromboembolism and major bleeding in patients treated for venous thromboembolism. *Thromb Haemost*. 2013;110(4):834-843.
11. Iorio A, Kearon C, Filippucci E, et al. Risk of recurrence after a first episode of symptomatic venous thromboembolism provoked by a transient risk factor: a systematic review. *Arch Intern Med*. 2010;170(19):1710-1716.
12. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3(4):692-694.
13. Prandoni P, Lensing AW, Piccoli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood*. 2002;100(10):3484-3488.