American Journal of Gastroenterology
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Published by Blackwell Publishing

ISSN 0002-9270
doi: 10.1111/j.1572-0241.2007.01477.x

Prognostic Factors in Noncirrhotic Patients With Splanchnic Vein Thromboses

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OBJECTIVES AND METHODS: Splanchnic vein thrombosis (SVT), not associated with cancer or liver cirrhosis, is a rare event and scanty data are available on its natural history, long-term prognosis, and treatment. In this study 121 SVT patients consecutively seen from January 1998 to December 2005 were included and 95 of them were followed up for a median time of 41 months. Screening for thrombophilic factors was performed in 104 patients. New thrombotic or bleeding episodes were registered and anticoagulant therapy was performed according to preestablished criteria.

RESULTS: SVT was an incidental finding in 34 (28.1%) patients; 34 (28.1%) presented with abdominal infarction; 39 (32.2%) had bowel ischemia or acute portal vein thrombosis; 14 (11.6%) had bleeding from portal hypertensive sources. Survival rates at 1, 3, and 7 yr were 95%, 93.3%, and 89.6%, respectively; 87.5% of deaths occurred at onset of SVT as complications of intestinal infarction. Patients with isolated portal vein thromboses had symptoms and intestinal infarction in 16/41 (39%) and 0/41 (0%) of the cases, respectively, whereas superior mesenteric vein thromboses, isolated or not, were associated with symptoms and intestinal infarction in 69/75 (92%) and 34/75 (45%), respectively.

During the follow-up 14 (14.7%) suffered from 39 episodes of gastrointestinal bleeding with no deaths. A previous gastrointestinal bleed was associated with new hemorrhagic events during follow-up.

New venous thrombotic episodes occurred in 10 of 95 patients (10.5%), of which 73% were in the splanchnic area. Seven out of these 10 patients had a chronic myeloproliferative disease (MPD) and none was on anticoagulation.

CONCLUSIONS: Anticoagulant therapy was effective to obtain recanalization of acute SVT in 45.4% of patients and preserved patients from recurrent thrombosis when given lifelong.

(Am J Gastroenterol 2007;102:2464–2470)

INTRODUCTION

Thromboses of the portal, splenic, and mesenteric veins or splanchnic vein thromboses (SVT) are rare disorders in the absence of abdominal cancer or liver cirrhosis. In the past, SVT were suspected mostly in patients presenting with recurrent bleeding from esophageal varices without overt liver disease (1). In the last decade the availability of advanced imaging procedures such as Doppler ultrasound, computer tomography (CT), and magnetic resonance imaging (MRI) allowed a better diagnosis of SVT in a large number of clinical settings ranging from fortuitous asymptomatic occlusions to acute abdomen. Moreover, the possibility of diagnosing SVT earlier results in a more prompt and effective therapy that translates in decreased morbidity and mortality (2, 3).

In similarity with thrombosis in other venous districts, SVT may develop according to a complex interplay of local or systemic factors including inherited or acquired thrombophilia (4–7). Given the rarity of SVT, studies comparing the different therapeutic options (thrombolysis, anticoagulation, thrombectomy) are not available, but anticoagulation is widely accepted as first choice therapy with strong clinical evidence to support its use in acute presentations. On the other hand, long-term prognosis, morbidity, and mortality of SVT are largely unknown and no data are available to identify those patients in which lifelong anticoagulation is necessary to prevent recurrent thrombosis. We describe our experience

on a large series of SVT patients with particular focus on prognostic factors and natural history.

PATIENTS AND METHODS

Demographics

The study was carried out on 121 patients seen at the Cardarelli Hospital in Naples (Italy) between January 1998 and December 2005: ninety-two were consecutive patients with new SVT whereas 29 were diagnosed with SVT before 1998. Our hospital is a tertiary referral center for gastrointestinal and liver emergencies that serves a population of about 3 million inhabitants and holds the liver transplantation center of Campania, a region of Italy with a population of 5.7 million. All the patients included were of white origin and came from the described geographical area.

The date of enrolment in the study was considered that of the clinical event leading to the diagnosis of SVT or that of the first imaging procedure showing SVT. SVT was diagnosed by Doppler ultrasound and confirmed by CT or MRI and/or angiography as required. SVT was considered recent in patients with an acute clinical onset or when symptoms developed <60 days prior to hospital admission and in the absence of clinical, radiological, or endoscopic evidence of portal hypertension or of collateral circulation (8, 9). Portal cavernoma was defined by the presence of multiple, millimetric channels that replaced the thrombosed portal trunk. Concomitant abdominal or extraabdominal cancer was excluded by imaging studies. Liver cirrhosis was excluded by normal clinical, laboratory, and imaging data or from liver histology. One hundred forty-three cirrhotic patients with SVT among 1,323 patients with liver cirrhosis admitted in the same period were excluded.

Precipitating factors for SVT (abdominal surgery, acute inflammation or sepsis, trauma, pregnancy, use of contraceptive drugs) were recorded. A thrombophilia screen was performed in 104 patients: this included assessment of protein C, protein S, antithrombin, factor V Leiden, prothrombin 20210 G→A, antiphospholipid antibodies (anticardiolipin antibodies and lupus anticoagulant), and fasting plasma homocysteine as previously described (10). Overt chronic myeloproliferative diseases (MPDs) (polycythemia vera, essential thrombocythemia, idiopathic myelofibrosis) were diagnosed according to established criteria (11–14). The tyrosine kinase mutation, Val617Phe, in the JH2 pseudo-kinase domain of the Janus kinase-2 (JAK2 V617F) gene was evaluated in 90 patients (15, 16). Ninety-five of 121 patients were followed up every 6 months with clinical, biochemical, and ultrasound evaluation. Upper gastrointestinal endoscopy was performed every 1–2 yr (17). All recurrent thrombosis, gastrointestinal bleeding, and adverse events of anticoagulant therapy were registered.

Management

From 1998 all SVT patients presenting with abdominal pain due to mesenteric venous infarction or ischemia or acute portal vein thrombosis were started on low molecular weight heparin 200 UI/kg a day for 7–10 days followed by oral anticoagulation for 6 months. Oral anticoagulation was maintained lifelong in the following cases: in patients submitted to intestinal resection for intestinal infarction, in patients who achieved incomplete recanalization of thrombus, and in patients with inherited thrombophilia. Patients presenting with gastrointestinal bleeding after 1998 were treated preferentially with endoscopic hemostatic procedures (sclerotherapy, band ligation, or cyanoacrylate glue) and did not receive anticoagulation therapy. Patients with esophageal varices at risk of bleeding received nonselective beta-blockers as prophylaxis unless contraindicated (18).

STATISTICAL ANALYSIS

For categorical variables the χ^2 test without or with exact correction was applied. The independent-samples *t*-test procedure was used to compare means for two groups of cases after checking for equal variance. Kaplan-Meier's estimation was used to calculate the survival rate at 1, 3, 5, and 7 yr of follow-up. The continuous data are presented as mean and standard deviation, and *P* value 2-tailed less than 0.05 was considered statistically significant. All analyses were run using SPSS 15.0.0 (SPSS Inc., Chicago, IL).

RESULTS

Of the 121 patients 59 were men and 62 women with a median age of 45 (2–83) yr. SVT was an incidental finding in 34 (28.1%) patients; 34 (28.1%) patients presented with an acute abdomen due to infarction (mesenteric in 32 and splenic in 2); 39 (32.2%) patients presented with severe abdominal pain due to bowel ischemia or acute portal vein thrombosis; 14 (11.6%) patients presented with bleeding from portal hypertensive sources. With regards to occlusion sites, 44 (36.4%) patients had mesenteric and portal vein thrombosis, 10 (8.3%) patients had a splenic, mesenteric, and portal thrombosis, 41 (33.9%) patients had an isolated portal vein thrombosis, 5 (4.1%) patients had portal and splenic thrombosis, and 21 (17.3%) had an isolated mesenteric vein thrombosis.

An isolated portal vein thrombosis was frequently asymptomatic (25/41; 61%); abdominal pain was the main clinical feature in the remaining cases and no intestinal infarction occurred in these patients. Superior mesenteric vein thrombosis either in isolation or in association with portal involvement was mostly acutely symptomatic (69/75, 92%) with intestinal infarction in 34/75 (45%) cases. A portal cavernoma was found in 60 out of 121 cases (50%) at presentation: in 92.8% of patients with bleeding, in 46.1% of patients with abdominal pain/infarction, and in 50% of patients with incidental SVT.

Seventeen patients (14%) had a familial history of venous thrombosis and 19 (15.7%) had a previous episode of venous thrombosis. Risk factors for thrombosis identified in our patients are listed in Table 1. Seventy-five (72.1%) patients had at least one risk factor for venous thrombosis, 28 (26.9%)

Table 1. Prevalence of Acquired and Inherited Thrombophilic Risk Factors in 104 SVT Patients Studied

ACQUIRED	
Systemic	
MPD	18 (17.3%)
JAK2 mutation*	12 (13.3%)
Drugs	12 (11.5%)
Oral contraceptives	11
Thalidomide	1
Infection/inflammation	3 (2.9%)
CMV	2
SLE	1
Hyperhomocysteinemia	16 (15.4%)
ACA	1 (0.9%)
Local	
Surgery	20 (19.2%)
Splenectomy	12
Cholecistectomy	12
Gastroresection	2
Aortic aneurysm	1
Umbilical vein catheterization	1
Renal transplantation	1
Cesarean section	1
Infection/inflammation	9 (8.6%)
Pancreatitis	5
Cholangitis	2
Diverticolitis	1
Ulcerative colitis	1
INHERITED	
Congenital hepatic fibrosis	5 (4.8%)
Protein C deficiency	4 (3.8%)
AT	1 (0.9%)
FVL	7 (6.7%)
PTHR 20210	14 (13.5%)

*Performed in 90 patients; MPD = myeloproliferative disease; CMV = cytomegalovirus; SLE = systemic lupus erythematosus; ACA = anticardiolipin antibodies; AT = antithrombin; FVL = factor V Leiden; PTHR 20210 = mutation 20210 of prothrombin gene.

patients had two or more risk factors. An overt MPD was present in 18/104 patients (17.3%). Twelve out of 90 patients (13.3%) carried the heterozygous JAK2 V617F mutation, 9 with an overt MPD and 3 without MPD.

Outcome

Of 32 patients with intestinal infarction, 1 died before intervention and 31 underwent intestinal resection. Four of the 32 patients were submitted to surgery twice for early intestinal reinfarction. Five patients died from perioperative complications. One of the 2 patients with splenic infarction was submitted to splenectomy. The overall mortality for intestinal infarction was 18.7%. Of the 39 SVT patients admitted because of abdominal pain, 31 received low molecular weight heparin, 4 were submitted to local thrombolysis, 3 started oral anticoagulation because of delayed diagnosis, and one received no therapy. None of these patients needed surgery.

Of the 14 patients that presented with gastrointestinal bleeding (11 esophageal varices, 2 gastric varices, 1 hypertensive gastropathy), 7 were treated by endoscopic techniques (4 sclerotherapy and 3 band ligation), 1 had esophageal transection, 1 had splenectomy, and 2 had surgical portal systemic shunts. None of these patients died because of bleeding.

FOLLOW-UP

Ninety-five out of 121 patients were followed up (median 41 months, range 3–500 months) in our center (18 were lost at follow-up, 6 were deceased at diagnosis, 2 were submitted to surgical portal systemic shunts) (Fig. 1). Forty-one patients (43.2%) received lifelong oral anticoagulation according to the established criteria (Fig. 1): 20/22 patients with previous abdominal infarction (1 patient refused and 1 patient received antiplatelet agents); 18/32 patients with abdominal pain at presentation: 12 received warfarin for only 6 months, 2 patients were not on oral anticoagulation (1 for contraindications to anticoagulant therapy and another 1, seen elsewhere at presentation, received no further therapy after initial thrombolysis). Only 3 patients with asymptomatic SVT received anticoagulation for the presence of inherited risk factors.

Overall, of 21 patients considered to have recent SVT, 10 (45.4%) achieved a complete recanalization with anticoagulation. All 10 patients but 2 (1 with inherited thrombophilia and 1 with recurrent venous thrombosis) stopped anticoagulation after 6 months: in one patient portal thrombosis recurred after 22 months. Minor bleeding episodes (1 epistaxis and 1 gum hemorrhage) were registered during anticoagulation therapy in two patients and required only warfarin dose adjustment.

Bleeding Episodes

Fourteen (14.7%) patients suffered 39 recurrent episodes of gastrointestinal bleeding: 6 patients bled once, 1 patient twice, 4 patients thrice, and 3 more than three times. The sources of the first bleeding episode during follow-up were esophageal varices in all patients whilst gastric and ectopic varices were implicated in the ensuing episodes. Rebleeding was more frequent in patients with bleeding at presentation of SVT (57.1%) compared to patients who had never bled (4.9%) ($P < 0.0001$) (Table 2). Despite the number of rebleeding episodes, no patients died because of it. One patient died of myocardial infarction 2 wk after admission for bleeding esophageal varices. No patient in this group was on anticoagulation.

Upper gastrointestinal endoscopy for evaluation of variceal development was performed every 1–2 yr in 42 patients with evidence of portal and/or splenic thrombosis: 20 had no varices (F0) (47.7%), 8 (19.0%) presented small varices (F1), and 14 (33.3%) had medium-large varices (F2-F3) at presentation. Patients without esophageal varices at presentation did not develop any during the follow-up; 3 out of 8 patients with F1 varices progressed to F2–F3 and one of them bled. Five out of 14 patients with F2–F3 varices complained of gastrointestinal bleeding.

Thrombotic Episodes

Ten of the 95 patients (10.5%) presented eleven new venous thrombotic episodes: 2 mesenteric infarctions, 2 splenic infarctions, 3 mesenteric ischemias, 1 deep vein thrombosis of the leg, 1 deep vein thrombosis of the arm, 1 spontaneous

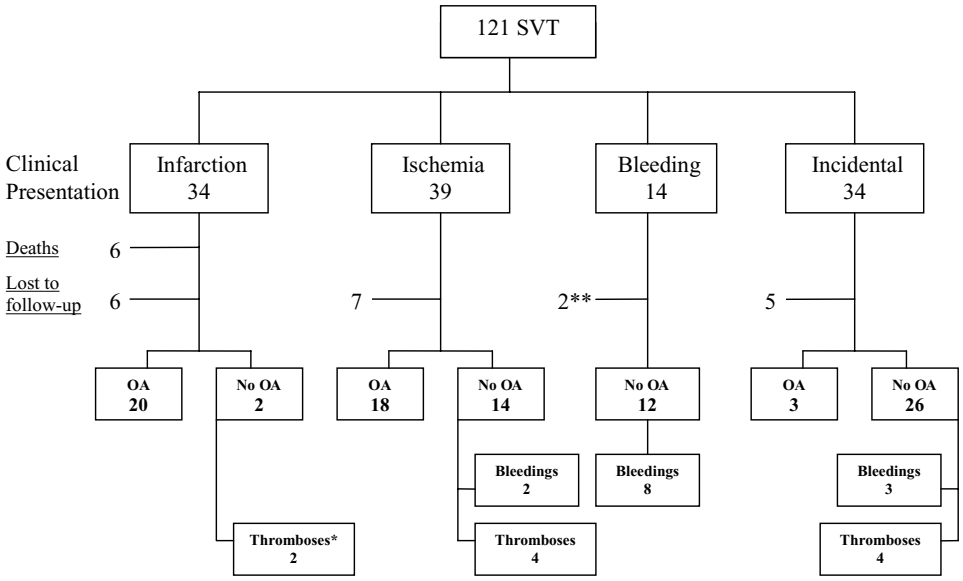

Figure 1. Clinical features and follow-up of patients with SVT: infarction = 32 mesenteric infarctions, 2 splenic infarctions; ischemia = abdominal pain due to acute venous mesenteric ischemia or acute portal vein thrombosis; bleeding = gastrointestinal bleeding due to portal hypertension; incidental = SVT in otherwise asymptomatic patients. OA = oral anticoagulant therapy; *1 patient with a bleeding episode too; **excluded because of portal-systemic shunts.

jugular vein occlusion, and 1 portal mesenteric rethrombosis after complete recanalization. Moreover, four episodes of arterial thrombosis (2 cerebral ischemias, 2 myocardial infarctions) occurred in four patients with MPD. The incidence of new venous thromboses was not different if the patients were split according to the modality of initial SVT presentation and the extension of thrombosis. Thrombosis did not recur in the group that presented with bleeding. MPD occurred in 7/10 (70%) patients with and 11/85 (12.9%) without recurrent venous thrombosis ($P < 0.0001$). One patient with myelofibrosis died from intestinal infarction caused by the extension of portal thrombosis to the mesenteric vein. She was not on anticoagulation therapy because of a previous episode of bleeding from esophageal varices.

Recurrent venous thrombosis occurred in 10 (18.5%) nonanticoagulated patients and in none of the anticoagulated patients (Table 3).

Mortality

Six patients died at diagnosis for complications of mesenteric infarction, 7 further patients died by the end of follow-up,

Table 2. Characteristics of 95 Patients With and Without Recurrent Bleeding Events During Follow-Up

	Recurrent Bleeding N = 14	No Recurrent Bleeding N = 81	*P* Value
Mean age (SD), years	29.3 ± 28.6	44.4 ± 14.8	0.07
Male, N (%)	6 (42.9)	44 (54.3)	0.43
Inherited thrombophilia, N (%)	1 (7.1)	33 (40.7)	0.02
MPD, N (%)	4 (28.6)	14 (17.3)	0.32
Modality of first presentation, N (%)			<0.0001
Incidental finding	3 (21.4)	26 (32.1)	
Mesenteric infarction or abdominal pain	3 (21.4)	51 (63)	
Bleeding from esophageal varices	8 (57.1)	4 (4.9)	
Kind of thrombosis, N (%)			0.24
Portal	6 (42.9)	34 (42)	
Porto-mesenteric and or splenic	8 (57.1)	34 (42)	
Mesenteric	0 (0)	13 (16)	

SD = standard deviation; MPD = myeloproliferative disease.

Table 3. Characteristics of 95 Patients With and Without Recurrent Venous Thrombotic Events During Follow-Up

	Recurrent Venous Thrombosis N = 10	No Recurrent Venous Thrombosis N = 85	*P* Value
Mean age (SD), years	42.6 ± 16.9	42.1 ± 18.3	0.93
Male, N (%)	4 (40)	46 (54.1)	0.40
Inherited thrombophilia, N (%)	3 (30)	31 (36.5)	0.68
MPD, N (%)	7 (70)	11 (12.9)	<0.0001
Modality of first presentation, N (%)			
Incidental finding	4 (40)	25 (29.4)	0.46
Mesenteric infarction or abdominal pain	6 (60)	48 (56.5)	
Bleeding from esophageal varices	0 (0)	18 (14.1)	
Kind of thrombosis, N (%)			
Portal	4 (40)	36 (42.4)	
Porto-mesenteric and or splenic	6 (60)	36 (42.4)	
Mesenteric	0 (0)	13 (15.3)	0.42
Anticoagulation, N (%)	0 (10)	39 (45.9)	0.005

SD = standard deviation; MPD = myeloproliferative disease.

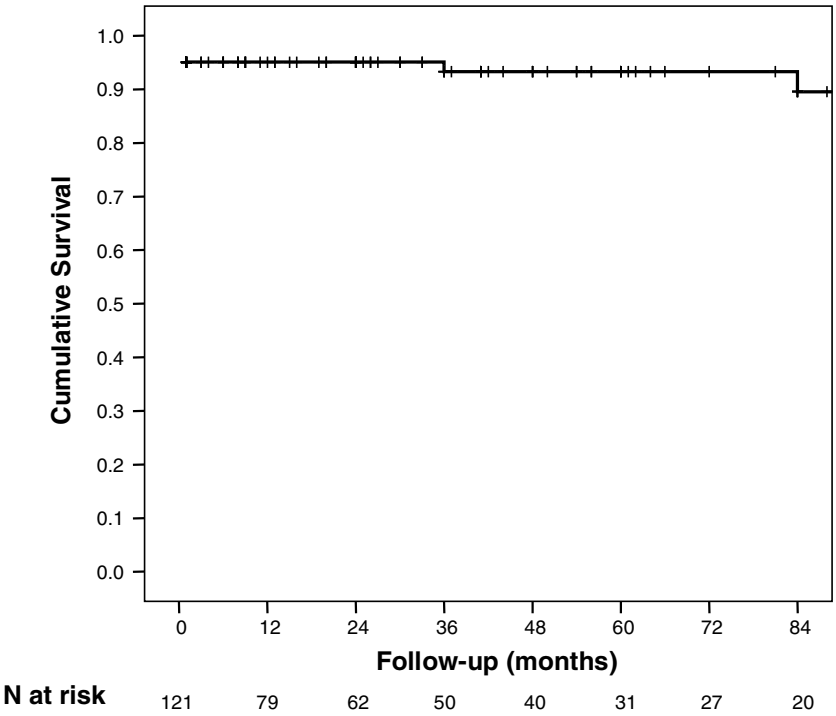

Figure 2. Kaplan-Meier curve for SVT-related mortality.

1 for causes related to SVT (1 mesenteric infarction) and 5 for unrelated diseases (2 rectal adenocarcinomas, 1 laryngeal carcinoma, 1 cholangiocarcinoma and 1 pulmonary edema, 1 myocardial infarction). Survival rates at 1, 3, and 7 yr were 95%, 93.3%, and 89.6%, respectively (Fig. 2).

DISCUSSION

Clinical manifestations and natural history of SVT are strongly affected by extension and rapidity of thrombus formation. As described in other series (2, 7, 8, 19) thrombosis involved more than one abdominal vein in about 50% of our patients whereas isolated portal and mesenteric thrombosis account for 33.9% and 17.3% of cases, respectively. Moreover, signs of old thrombosis (cavernoma) were already present in 50% of patients at diagnosis. Although a portal cavernoma can develop within days (20) in an experimental model, our data suggest that an acute onset does not always mean a recent thrombosis.

The main determinant of acute symptomatic presentation is the involvement of mesenteric vein or the extension of thrombosis beyond portal vein. Mesenteric vein thrombosis causes intestinal ischemia of small bowel that if not early recognized and promptly treated (21–23) progresses to intestinal infarction. Amongst 73 SVT admitted for acute abdominal pain, 46.7% already had an intestinal infarction requiring surgical treatment. The intestinal infarction presented in the majority of the cases at diagnosis of SVT and was the main cause of mortality in our patients, accounting for 87.5% of deaths. In the remaining patients the disease had a more benign course with a very low mortality: only two patients died during the follow-up, the first from myocardial infarction after an episode of bleeding from esophageal varices and the second from intestinal infarction. SVT progressed either because of complications of portal hypertension or new episodes of splanchnic and extrasplanchnic thrombosis. In fact, if we considered the group of patients with incidental diagnosis of SVT, clinical events occurred in 27% of patients (3 episodes of bleeding and 4 of thrombosis).

As far as bleeding episodes are concerned, 14 of 95 patients in follow-up experienced 39 episodes of gastrointestinal hemorrhage. No patient died because of bleeding and as expected (9, 21, 24) this good outcome could be attributed to the well-preserved liver function and the efficacy of endoscopic procedures. The new episodes of bleeding were more frequent in patients with previous bleeding at SVT diagnosis compared with those who had never bled. Gastrointestinal bleeding due to portal hypertension does not feature early in the natural history of SVT since portal cavernomatous transformation was already present in 92.8% of bleeding patients. Moreover, the presence of esophageal varices at diagnosis predicted further variceal enlargement or bleeding during follow-up whereas patients without varices did not develop further varices along the same time span. The development of different collateral vessels, their location, and efficiency can explain this behavior as in other models of portal hypertension.

Ten patients experienced 11 episodes of new venous thrombosis, of which 73% occurred in the splanchnic area, and one patient died. Only the presence of chronic MPD and lifelong anticoagulation were significantly associated with

the risk of rethrombosis. The presence of genetic thrombophilic factors did not influence the rate of rethrombosis in our patients, obviously so because we opted to anticoagulate these patients "*a priori*" on the basis that patients with persistent risk factors (inherited thrombophilia) have a persistent risk of rethrombosis. On the other hand, a study with a nonanticoagulated control group of patients with SVT will never be done as these patients will reasonably be offered lifelong anticoagulation.

Chronic myeloproliferative disorders predispose patients to either arterial and venous thrombosis or bleeding episodes and are the main risk factors of SVT in western countries. Interestingly, 70% of patients with recurrent venous thrombosis had concomitant MPD and a further four episodes of arterial thrombosis (2 myocardial infarctions and 2 cerebral ischemias) were also registered in these patients. These data reinforce the necessity to plan specific studies addressing the efficacy of anticoagulation therapy in patients with MPD.

A general consensus exists on the necessity to offer early anticoagulation in SVT patients presenting acutely. According to our definition only 21 of 95 patients presented with a recent thrombosis: anticoagulation achieved a complete recanalization in 45.4% of them, a figure lower than the 80.6% reported by Condat *et al*. (8), in which not only complete but also partial recanalization was considered. Nevertheless we think the efficacy of acute anticoagulation should be judged not only in terms of recanalization but also of resolution of the acute clinical scenario and prevention of abdominal infarction. It is unclear which SVT patients should be offered long-term anticoagulation. We applied existing guidelines for deep vein thrombosis and pulmonary embolism in our patients bearing in mind that a recurrent SVT could be fatal. Therefore we offered lifelong anticoagulation to SVT patients presenting with intestinal infarction or acute abdominal pain that did not achieve recanalization of the clot and to SVT patients with inherited thrombophilic defects. Even if questionable and not validated, our policy on long-term anticoagulation effectively preserved SVT patients from rethrombosis. New episodes of bleeding due to portal hypertension during the follow-up occurred only in patients not receiving lifelong anticoagulation. It could be argued that anticoagulation prevents thrombosis progression, thus preserving patients from the complications of portal hypertension.

In conclusion, our survey shows that SVT can be diagnosed much earlier nowadays with better imaging techniques. Extension of the thromboses into the superior mesenteric vein is associated with intestinal infarction and adverse outcome. A previous bleed from esophageal varices predicts new hemorrhagic events while the existence of a chronic MPD predicts new thrombotic events. Anticoagulant therapy yielded recanalization of acute SVT in half of the cases and protected the patients from recurrent or progressive thromboses.

STUDY HIGHLIGHTS

What Is Current Knowledge

- Natural history and short to medium term prognosis is poorly known in nonneoplastic and noncirrhotic splanchnic vein thrombosis.

What Is New Here

- Prospective information on natural history of splanchnic vein thrombosis.
- Previous episodes of esophageal bleeding or a portomesenteric or a splenic thrombosis are strong predictors of recurrent bleeding.
- Chronic myeloproliferative disorders and oral anticoagulation are respectively positive and negative predictors of re-thrombosis.

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Received January 20, 2007; accepted June 16, 2007

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CONFLICT OF INTEREST

Guarantor of the article: Lucio Amitrano, M.D.
Specific author contributions: Lucio Amitrano and Maria Anna Guardascione: study planning, study conducting, and drafting manuscript. Mariano Scaglione and Luigia Romano: radiological procedures. Luca Pezzullo: bone marrow biopsies and hematological follow-up. Nicola Sangiuliano and Mariano F. Armellino: patient management and abdominal surgery. Francesco Manguso: statistical evaluation. Maurizio Margaglione and Elvira Grandone: genetic testing. Luigi Iannaccone: coagulation testing. Paul R.J. Ames: anticoagulation planning and follow-up. Antonio Balzano: study supervision.
Financial support: None.
Potential competing interests: None.