REVIEW ARTICLE

How to treat patients with splanchnic vein thrombosis: recent advances

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ABSTRACT

Splanchnic vein thrombosis (SVT) is an unusual-site venous thromboembolism that includes portal, mesenteric, and splenic vein thrombosis as well as the Budd–Chiari syndrome. SVT is a relatively rare disease (portal vein thrombosis and Budd–Chiari syndrome are, respectively, the most and the least common presentations); roughly one-third of the cases are detected incidentally, and liver cirrhosis and solid cancer represent the main risk factors. Once SVT is diagnosed, careful patient evaluation should be performed to assess the stage, grade, and extension of the thrombosis, as well as the risks and benefits of the anticoagulation regimen. Anticoagulant therapy is effective in SVT treatment and is associated with high rates of vein recanalization, low rates of thrombosis progression or recurrence, and an acceptable rate of bleeding complications. Most available data come from observational studies in patients with liver cirrhosis–related SVT receiving low-molecular-weight heparin or vitamin K antagonists. Data on the use of direct oral anticoagulants are increasing and promising. In selected patients and in specialized centers, interventional procedures may be considered in adjunction to anticoagulation in the cases of mesenteric or extensive SVT, intestinal ischemia, or in the patients whose condition deteriorates despite adequate anticoagulant therapy. In this narrative review, we summarize the available data regarding anticoagulation in patients with SVT, identify specific subgroups of patients who may achieve the greatest benefits from anticoagulant therapy, and provide practical advice for clinicians caring for these patients.

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Introduction Splanchnic vein thrombosis (SVT) is generally defined as an unusual-site vein thrombosis and includes portal, mesenteric, or splenic vein thrombosis, and the Budd–Chiari syndrome (BCS).[1] SVT is a relatively rare disease, with incidence rates at least 25 times lower than those of usual-site venous thromboembolism (VTE).[2] Roughly one-third of the cases are incidentally detected during abdominal imaging performed for other reasons, and liver cirrhosis and solid cancer represent the main risk factors for SVT development.[2,3]

While the beneficial effects of anticoagulation on vein recanalization and thrombus progression or recurrence may be expected, its safety profile may be uncertain given the increased perceived risk of portal hypertension–related bleeding. However, anticoagulation improves splanchnic hemodynamics and may reduce the said risk thanks to vein recanalization. Recent data support this hypothesis and show that the incidence of both recurrent VTE and major bleedings was the lowest during anticoagulation, increased after treatment discontinuation, and was the highest in never-treated patients.[4] These results were confirmed even in specific subgroups of patients at a higher risk, such as those with solid cancer, liver cirrhosis, and incidentally detected SVT.[4]

Despite the fact that several observational studies and a few randomized controlled trials (RCTs) have been conducted over the last years in the attempt to fill the knowledge gap, therapeutic management of SVT still remains heterogeneous, current treatment recommendations vary widely across clinical practice guidelines, and every day clinicians have to struggle with the decision of which patients should be treated and which anticoagulant regimen should be administered.[1,5-9]

The objectives of this narrative review are to report the available evidence on the management of anticoagulation in patients with SVT, to identify specific subgroups of patients who may achieve the greatest benefits from anticoagulant therapy, and to provide practical advice for clinicians caring for these patients.

Medical treatment of acute splanchnic vein thrombosis

Once SVT is diagnosed, the stage of thrombosis has to be identified. Distinguishing an acute SVT from a chronic one is challenging, but it has relevant clinical and therapeutic implications.[2] Acute SVT is characterized by the presence of a recent thrombus involving 1 or more splanchnic veins without collateral portosystemic shunts or portal cavernoma that usually cause specific symptoms and signs. It is associated with a high risk of thrombotic and bleeding complications and a high mortality rate.[2,10] For this reason, a prompt therapeutic evaluation has to be performed.[11]

Anticoagulant treatment represents the backbone of acute SVT management and is strongly suggested in symptomatic patients with this disease (TABLE 1) to avoid bowel ischemia, thrombosis extension and recurrence, cavernous transformation, or chronic portal hypertension.[11-13] After the first 6 to 12 months from thrombus development, vein recanalization becomes unlikely.[14,15] Several observational studies and few RCTs and meta-analyses explored the role of anticoagulation, mainly in patients with liver cirrhosis–related acute SVT.[16-18] A 6-month enoxaparin treatment at a therapeutic (ie, 1 mg/kg twice daily) or intermediate (ie, 1.5 mg/kg once daily) dose resulted in vein recanalization in roughly 80% of the patients, with low rates of thrombosis progression and no major bleedings.[19] A recent small randomized trial comparing the efficacy and safety of a nadroparin sodium–warfarin scheme for 6 months versus no treatment in 64 patients with liver cirrhosis–related portal vein thrombosis showed a higher rate of vein recanalization (62.5% vs 34.4%), lower rate of thrombus progression (15.6% vs 40.6%), and no differences in terms of bleeding complications in the anticoagulated patients than in the untreated patients.[20] The results of the available observational studies confirm those of RCTs, and the efficacy and safety of anticoagulant therapy appears to be maintained also in the patients with risk factors other than liver cirrhosis (eg, solid cancer or myeloproliferative neoplasms).[4,17,21-23] For this reason, international guidelines mainly suggest low-molecular-weight heparin (LMWH) and vitamin K antagonists (VKAs), such as warfarin with an international normalized ratio (INR) therapeutic range between 2.0 and 3.0.[1,6,11,14,15] Of note, early initiation of anticoagulation was shown to be associated with a higher thrombosis resolution rate and lower recurrence of thrombotic events, with a similar risk of bleeding and mortality after endoscopic variceal band ligation.[24-26] In these cases, experts suggest to start anticoagulation with a prophylactic or intermediate dose of LMWH within 14 days from the diagnosis and in the absence of active bleeding or other contraindications, and to increase the LMWH dose to a therapeutic one or switch to an oral anticoagulant after proper management of esophageal varices has been achieved.[27]

Although international societies recommend anticoagulation in patients with acute SVT, the length of treatment is not well specified. As reported by a recent retrospective study, vein recanalization is achieved in 60% of the patients within the first 3 months, and this rate rapidly decreases thereafter.[28] On the other hand, thrombosis progression or recurrence may develop, respectively, in 20% and 40% to 60% of the patients after a mean time of 4 months from anticoagulant treatment discontinuation.[28-32] Careful evaluation of thrombotic risk factors is therefore mandatory before making a decision regarding the treatment duration, and all available guidelines suggest 3 to 6 months of anticoagulation if a transient / modifiable thrombotic risk factor is identified. In addition, long-term anticoagulation may be considered if there is a persistent risk factor or if SVT is unprovoked.[1,6,11,14,15] Furthermore, long-term or indefinite treatment is suggested in the patients with BCS.[11,15] Some authors argued a possible role of the grade and extension of the thrombus after the first months of anticoagulation and the need for liver transplantation in guiding treatment duration.[15,32-34] Even though data are scarce, long-term administration of low-dose LMWH (eg, prophylactic) appeared to ensure an acceptably low rate of thrombus progression in cirrhotic patients with SVT and may be considered to minimize the bleeding risk in the patients at a higher risk.[32,33]

A small number of patients included in the available studies received concomitant antiplatelet therapy. Data on the effectiveness and safety of this therapeutic approach are lacking and no guideline recommendations are available.[35]

Some clinical characteristics of SVT may make the therapeutic decision challenging. An incidentally detected SVT is diagnosed during routine abdominal imaging performed for other reasons in 1 out of 3 patients, and it is associated with a risk of recurrence and progression of thrombosis similar to that observed in acute SVT.[36-38] For this reason, incidentally detected SVT should be treated for at least 3 to 6 months, except for the patients with persistent or nonidentifiable risk factors or those with recurrent vein thrombosis, in whom long-term or indefinite treatment is suggested.[1,11] Similarly, thrombocytopenia may characterize patients with SVT, mainly when liver cirrhosis is the underlying risk factor. However, data regarding this scenario are scarce, no guideline recommendations are available, and the therapeutic decision actually has to be taken on a patient-by-patient basis, considering the fact that the dose of LMWH should be adapted to specific patient characteristics.[11]

FIGURE 1 presents our proposed therapeutic approach to the management of patients with acute SVT. Briefly, in the individuals with acute symptomatic or incidentally detected SVT, in the absence of active bleeding or other contraindications, parenteral anticoagulation at a low dose (eg, a prophylactic or intermediate dose of LMWH) should be started within 14 days from the diagnosis. When proper management of esophageal varices has been achieved, parenteral anticoagulation should be increased to therapeutic doses of LMWH or an oral anticoagulant should be started based on specific patient characteristics (eg, underlying risk factors, presence of liver or kidney failure, thrombocytopenia, a history of major bleeding). After the first 3 to 6 months of anticoagulation, the thrombotic and bleeding risks should be periodically reassessed to evaluate the need for a long-term treatment.

Medical treatment of chronic splanchnic vein thrombosis Chronic SVT is defined as a thrombosis lasting more than 6 months in the presence of abdominal venous collaterals or cavernous transformation of the portal vein.[2] However, the stage of SVT may only be approximated by the change in the characteristics of symptoms and signs over time or by the time that elapsed between the first radiological image indicating thrombosis and the previous one with no such signs, if available.[2] An important factor to consider is that vein recanalization may occur in less than a third of the anticoagulated patients with chronic SVT.[39] Conversely, a significant recurrence risk reduction has been reported in the anticoagulated individuals.[11,14,15,39] Due to the lack of clear evidence regarding the management of chronic SVT patients, the decision regarding treatment is often guided also by patients' preference, potential improvement in the quality of life, and costs.[11]

According to the European Association for the Study of the Liver guidelines, in chronic SVT triggered by a transient risk factor, long-term anticoagulant therapy should be considered in patients with a history of intestinal ischemia or recurrent thrombosis.[1] Conversely, if a permanent risk factor is present in chronic SVT patients, long-term anticoagulant treatment should be considered independently of the extension or site of SVT.[1]

Recent guidelines of the International Society on Thrombosis and Haemostasis (ISTH) recommend to carefully evaluate the use of anticoagulant therapy on a case-by-case basis, and to consider a watchful approach in selected patients with chronic SVT to minimize the bleeding risk.[11] The same panel of experts acknowledged the fact that, as in the case of usual-site VTE, reduced doses of LMWH or direct oral anticoagulants (DOACs) may be used to minimize the bleeding risk.[11]

Our proposed therapeutic approach to the management of patients with chronic SVT is shown in FIGURE 1. In these cases, the decision between a watchful approach and long-term anticoagulation should be mainly driven by the assessment of the risk of thrombosis recurrence or progression and the risk of bleeding associated with the underlying risk factor for SVT. When anticoagulation is started, a periodic re-evaluation of the need for anticoagulant therapy should be performed and guided by patient characteristics.

Data on direct oral anticoagulants Patients with SVT were generally excluded from major RCTs on DOACs; therefore, this class of drugs has not been specifically approved for this indication. Nevertheless, observational studies have shown at least the same efficacy and superior safety of DOACs, as compared with traditional anticoagulants, when used to treat usual-site VTE. Moreover, DOACs have additional advantages over other anticoagulants, such as the oral administration and the lack of necessity of strict laboratory monitoring.[40-43] However, DOACs should be used with caution in the cases of suspected malabsorption and bowel ischemia, which are conditions that could occur in SVT.[44] Furthermore, DOACs may carry a non-negligible risk of gastrointestinal bleeding as compared with warfarin in specific populations, and their use is not allowed in patients with liver cirrhosis and a Child–Pugh class B (rivaroxaban) or C (all DOACs), which is often associated with SVT.[2,3,45,46] On the other hand, several meta-analyses of observational studies showed a similar effectiveness and a lower bleeding risk for DOACs, as compared with VKAs, in patients with cirrhosis and a Child–Pugh class A or B, even when esophageal varices were present.[47-49]

Few and mainly observational studies are available on the use of DOACs in patients with SVT; however, despite the paucity of data, their administration has been rapidly increasing over time.[50,51] Based on these studies as well as on data from patients with usual-site VTE, a recent ISTH position statement suggested treatment with full therapeutic doses of DOACs in noncirrhotic patients with symptomatic or incidentally detected acute SVT without signs of active bleeding or other contraindications, and recommended DOACs or LMWH in patients with cancer-associated symptomatic acute SVT.[11] In the case of contraindications (eg, severe liver cirrhosis or kidney failure), poor tolerance of DOACs, or possible drug-to-drug interactions, LWMH or VKAs should be considered.[11] The Baveno VII criteria and the American Association for the Study of Liver Disease guidelines reported that the use of DOACs in patients with SVT can be considered and should be individualized based on patient characteristics (TABLE 1).[14,15]

These treatment recommendations are supported by the results of several studies, mainly of observational design.[50] One of the first prospective study that investigated the role of DOACs in this setting compared the administration of rivaroxaban and apixaban in unusual- (ie, splanchnic, ovarian, renal, and cerebral veins)

TABLE 1 Summary of recent guideline recommendations on anticoagulant therapy for splanchnic vein thrombosis (continued on the next page)

Patients	Additional characteristics	Anticoagulation regimens	Anticoagulation duration
Baveno VII guideline (2022)[15]			
PVT with cirrhosis	• Recent (<6 months), with lumen occlusion ≥50% or • Symptomatic or • Candidates for transplantation (C2)	• LMWH (C1) or • LMWH → VKAs (C1) or • LMWH → DOACs (C1) • DOACs to be used with caution in patients with Child–Pugh class B; not recommended in Child–Pugh class C (B2)	• At least 6 months (C1) • Until PVT recanalization in transplantation (C1) • Consider long-term therapy (C1)
	• Lumen occlusion <50% or • Thrombus progression in 1–3 months or • Mesenteric vein involvement (C2)		
PVT without cirrhosis	Recent (<6 months)	• LMWH → VKAs (B1) • DOACs can be considered (C2)	• At least 6 months (B1) • Long-term therapy recommended if there are permanent risk factors (B1) or to be considered if there are no underlying risk factors (B2)
	Chronic (>6 months)	–	• Long-term therapy recommended if there are permanent risk factors (B1) or to be considered if there are no underlying risk factors (B2)
BCS	–	–	• Long-term therapy (B1)
AASLD guideline (2021)[14]			
PVT with cirrhosis	Recent (<6 months) and main lumen occlusion ≥50%	• LMWH, VKA, or DOAC use should be individualized	• Anticoagulation should be considered
	Recent (<6 months) and small intrahepatic sub-branches or main lumen occlusion <50%		• No anticoagulation and serial imaging (3 months) are a reasonable approach • Anticoagulation in the case of thrombus progression
	Chronic complete thrombosis or cavernoma		• Target treatment at management of portal hypertension complication
PVT without cirrhosis	Recent (<6 months)		• Anticoagulation should be considered
BCS	–	–	• Anticoagulation should be administered
ISTH guideline (2020)[11]			
SVT with cirrhosis	Acute symptomatic or incidentally detected	• LMWH → VKAs • LMWH → DOACs	• At least 3–6 months • Longer course in the case of thrombotic progression or recurrence, unprovoked thrombosis, or persistent risk factors
	Chronic	–	• Case-by-case evaluation
SVT without cirrhosis	Acute symptomatic or incidentally detected	• DOACs • LMWH or VKAs to be considered	• At least 3–6 months • Longer course in the case of thrombotic progression or recurrence, unprovoked thrombosis, or persistent risk factors
	Chronic	–	• Case-by-case evaluation
SVT with cancer	Acute symptomatic or incidentally detected	• DOACs or LMWH • LMWH suggested in specific circumstances	• At least 3–6 months • Longer course in the case of thrombotic progression or recurrence, unprovoked thrombosis, or persistent risk factors
	Chronic	–	• Case-by-case evaluation
BCS	–	• LMWH • DOACs or VKAs to be considered	• Indefinite anticoagulation

TABLE 1 Summary of recent guideline recommendations on anticoagulant therapy for splanchnic vein thrombosis (continued from the previous page)

Patients	Additional characteristics	Anticoagulation regimens	Anticoagulation duration
EASL guideline (2016)[1]			
PVT with cirrhosis	–	–	• At least 6 months of therapeutic anticoagulation to be considered (B1) • Long-term anticoagulation to be considered in patients with superior mesenteric vein thrombosis, history of intestinal ischemia, or a need for liver transplantation (C2)
PVT without cirrhosis	Acute	LMWH (A1) → VKAs (B1)	• At least 6 months (A1)
BCS	–	–	• Indefinite anticoagulation in the absence of major contraindications (A1)

Abbreviations: AASLD, American Association for the study of Liver Disease; BCS, Budd–Chiari syndrome; DOACs, direct oral anticoagulants; EASL, European Association for the Study of the Liver; ISTH, International Society on Thrombosis and Haemostasis; LMWH, low-molecular-weight heparin; PVT, portal vein thrombosis; SVT, splanchnic vein thrombosis; VKAs, vitamin K antagonists

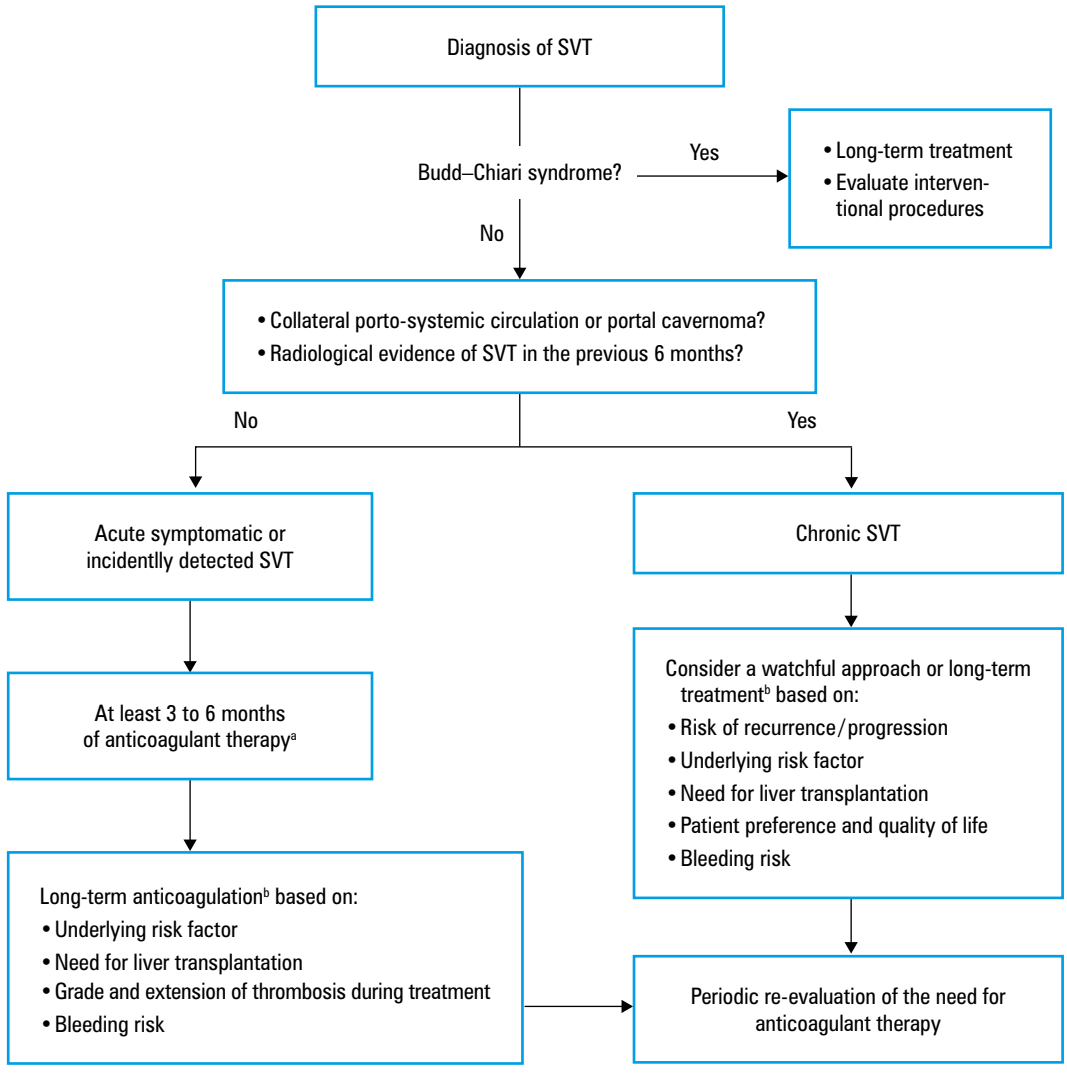

FIGURE 1 Suggested therapeutic management of patients with acute and chronic splanchnic vein thrombosis

a Anticoagulation may be started with LMWH at a prophylactic or intermediate dose within 14 days from diagnosis and in the absence of active bleeding or other contraindications; it may then be changed to a therapeutic dose of LMWH or switched to an oral anticoagulant as soon as possible after proper management of esophageal varices has been achieved.

b A reduced dose of parenteral/oral anticoagulants may be used to minimize the bleeding risk.[11]

Abbreviations: see **TABLE 1**

versus usual-site VTE (ie, pulmonary embolism and/or deep vein thrombosis).[52] While the rates of VTE recurrence and major bleeding were similar in all evaluated groups, the mortality rate was higher in the patients with unusual-site VTE than in the other group.[52] The results were similar in a small observational study including 50 cirrhotic patients with portal vein thrombosis who received edoxaban 60 mg once daily and danaparoid sodium or warfarin with an INR target of 1.5 to 2.[53] However, the largest observational study that evaluated the effectiveness and safety of rivaroxaban at a standard VTE dose for 3 months included 100 patients with noncirrhotic SVT. Nearly 80% of the patients achieved vein recanalization, 2.1% had recurrent VTE, and 2.1% experienced a major bleeding.[54]

Only 2 RCTs evaluating DOACs were performed in patients with SVT. In the study by Hanafy et al,[34] 80 cirrhotic patients with portal vein thrombosis after splenectomy were randomized to rivaroxaban at dose of 10 mg twice daily or warfarin with a standard therapeutic INR range. Rivaroxaban appeared to be more effective than warfarin in terms of complete (85% vs 45%, respectively) or partial (15% vs 0%) vein recanalization, recurrent portal vein thrombosis after treatment discontinuation (0% vs 22.2%), and major bleeding (0% vs 43.3%).[34]

Another trial randomized 111 patients with noncirrhotic chronic portal vein thrombosis to rivaroxaban 15 mg once daily or placebo.[55] Due to the higher rate of thrombotic events in the control group than in the treatment group, all patients were switched to rivaroxaban after the results of the interim analysis had been obtained. However, the small sample size, risk of bias, and potential for residual confounding factors hampered the interpretation of these results and further studies are needed to confirm them.

Data on DOACs in BCS are scarce and mainly come from 2 studies. The first one was a retrospective analysis of patients after endovascular intervention. In this study, dabigatran at a dose of 150 mg twice daily was administered to patients with VKA treatment failure (ie, labile INR, difficulties in maintaining a regular follow-up for VKA dose titration, or bleeding during VKA treatment).[56] At the 18-month follow-up, no differences in stent patency rates, major bleeding, and mortality have been identified between the patients treated with VKA and those treated with dabigatran. The second study included a retrospective cohort of 22 patients treated with different DOACs, with a median follow-up of 24 months. Despite a very small sample size, the rate of bleedings, complications of liver disease, and complete or ongoing response to treatment appeared to be similar in all treatment groups.[57]

Currently, an international multicenter prospective study (NCT03778502) is ongoing to evaluate the efficacy and safety of DOACs in the treatment of unusual-site VTE (ie, splanchnic, cerebral, retinal, ovarian, and renal vein thrombosis). The planned estimated sample size of this prospective observational study is 300 patients, all DOACs (ie, apixaban, dabigatran, edoxaban, rivaroxaban) may be administered, the target follow-up duration is 12 months, and the estimated study completion date is December 2024.

Interventional procedures Interventional procedures (ie, systemic or catheter-directed thrombolysis, mechanical thrombectomy, and transjugular intrahepatic portosystemic shunt [TIPS] implantation) may be a complementary therapeutic approach to anticoagulation.[58] These procedures may be considered in highly selected groups of patients treated in specialized centers, such as individuals with mesenteric or extensive SVT and signs of intestinal ischemia, or those whose condition deteriorates despite adequate anticoagulant therapy.[11,59-63] Of note, a non-negligible bleeding risk has been reported for these procedures, mainly related to gastrointestinal or intra-abdominal bleeding.[11,59-63]

More specifically, indirect thrombolysis via the mesenteric superior artery was shown to have a higher effectiveness and safety than systemic or catheter-directed thrombolysis in liver cirrhosis–related portal vein thrombosis.[64] The beneficial role of interventional procedures in terms of the patency rate appeared to be maintained also after a living-donor liver transplantation.[65] In acute noncirrhotic and nonmalignant portal vein thrombosis, the rate of vein recanalization in the patients undergoing an interventional procedure was higher than in those who only received anticoagulant treatment.[66] With respect to TIPS, 2 recent meta-analyses reported high rates of procedural success, 12-month vein patency, and survival. Also, the rate of vein recanalization was high; however, a potential beneficial role of concomitant anticoagulation in this outcome should be acknowledged.[67,68] The use of TIPS in noncirrhotic patients remains controversial, and most of the data come from patients with chronic thrombosis.[69-72]

In patients with BCS, a stepwise approach has been proposed, in which invasive procedures should be considered in the cases with no clinical and laboratory response after 2 weeks of anticoagulation.[73] Using this approach, the overall 1-year (96% vs 55%) and 5-year (89% vs 40%) survival rates were significantly higher than in the patients treated with anticoagulant therapy alone.[73] Some authors suggested to reduce the intensity of anticoagulation during interventional procedures to reduce the risk of bleeding. For example, in a retrospective study in patients undergoing TIPS or percutaneous angioplasty, low doses of LMWH were administered early after the procedure, and were increased to therapeutic ones 12 to 48 hours afterwards.[74] However, sound data are lacking, and treatment decisions have to be taken on a patient-by-patient basis.

Conclusions Prompt initiation of anticoagulant therapy should be considered in most patients with acute SVT, specifically those in whom the thrombotic risk exceeds the bleeding risk. The benefit of anticoagulant treatment in the patients with chronic SVT is less clear. The type, dose, and duration of anticoagulant therapy should be individualized based on the stage, grade, and extension of thrombosis, as well as on the presence of transient or persistent / permanent thrombotic risk factors.

ARTICLE INFORMATION

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