How to manage splanchnic vein thrombosis in patients with liver disease

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Liver cirrhosis and splanchnic vein thrombosis (SVT) are strictly correlated. Portal vein thrombosis, the most common location of SVT, is frequently diagnosed in liver cirrhosis (pooled incidence 4.6 per 100 patient-years), and liver cirrhosis is a common risk factor for SVT (reported in 24%-28% of SVT patients). In cirrhosis-associated SVT, anticoagulant treatment reduces mortality rates, thrombosis extension, and major bleeding, and increases the rates of recanalization, compared to no treatment. Achieving vessel recanalization improves the prognosis of cirrhotic patients by reducing liver-related complications (such as variceal bleeding, ascites, hepatic encephalopathy). Anticoagulation should be therefore routinely prescribed to cirrhotic patients with acute SVT unless contraindicated by active bleeding associated with hemodynamic impairment or by excessively high bleeding risk. Of note, early treatment is associated with higher probability of achieving vessel recanalization. The standard treatment consists of low-molecular-weight heparin, followed by oral anticoagulants (eg, vitamin K antagonists or direct oral anticoagulants), if not contraindicated by severe liver dysfunction. Cirrhotic patients with SVT should be treated long-term (especially if candidate for liver transplantation) since liver cirrhosis is a persistent risk factor for recurrent thrombosis. In this review, we discuss the management of SVT in patients with liver cirrhosis, with a focus on the anticoagulant treatment in terms of indications, timing, drugs, duration, and particular scenarios, such as gastroesophageal varices and thrombocytopenia.

LEARNING OBJECTIVES

- To identify which cirrhotic patients with SVT need anticoagulant treatment
- To choose the most appropriate anticoagulant treatment for cirrhotic SVT

CLINICAL CASE

A 55-year-old man with known liver cirrhosis presented to the emergency department with hematemesis from variceal bleeding. Endoscopic band ligation of esophageal varices was performed, and the patient was started on a beta-blocker. A computed tomogram showed a complete thrombosis of the main trunk of the portal vein. Blood tests showed mild thrombocytopenia (95×10^9/L) and normal kidney function (estimated glomerular filtration rate, 51 mL/min). The patient has Child-Pugh class A. You considered whether to initiate anticoagulation in this patient or not.

Introduction

Splanchnic vein thrombosis (SVT) refers to thrombosis of different veins that drain blood from the abdominal organs and includes portal vein thrombosis (PVT), mesenteric vein thrombosis, splenic vein thrombosis, and obstruction of the hepatic venous outflow (also known as Budd-Chiari syndrome).[1]

Portal vein thrombosis is the most common location in the SVT spectrum, with a pooled incidence in the cirrhotic population without hepatocellular carcinoma or previous abdominal surgery of 4.6 (95% CI, 3.5-5.8) per 100 patient-years.[2] The risk of developing PVT increases in parallel with the progression of liver cirrhosis, showing a pooled prevalence of 13.5% (95% CI, 9.5-18.2) in patients with Child-Pugh A and 23.7% (95%CI, 16.8-31.5) in patients with Child-Pugh B/C.[2]

Liver cirrhosis is a strong risk factor for SVT and is found in approximately 24%-28% of SVT patients.[3,4] In patients with liver cirrhosis, predictive factors for PVT include those related to the severity of portal hypertension (such as low platelet count or previous variceal bleeding), while hemostatic alterations (such as inherited thrombophilia or acquired hypercoagulability) and inflammatory biomarkers do not seem to predict the development of PVT.[5] Thus, peri-

odical assessment of the severity of liver disease and surveillance for hepatocellular carcinoma are recommended, while thrombophilia testing should not be performed in cirrhotic patients.[6]

Compared to other subgroups of SVT patients, cirrhotic patients with SVT exhibit higher rates of major bleeding (10.0 per 100 patient-years) and thrombotic events (11.3 per 100 patient-years) during follow-up.[3] Furthermore, the risk of developing adverse outcomes increases in parallel with the progression of liver cirrhosis.[7] In addition, liver cirrhosis is a known cause of intrahepatic portal hypertension, and the development of portosplenic vein thrombosis can further contribute to prehepatic portal hypertension.[8]

It has been reported that 34%-39% of cirrhotic patients with PVT present with gastrointestinal bleeding at onset.[9] Other clinical manifestations of acute PVT include abdominal pain and nonspecific symptoms, such as anorexia, nausea, vomiting, and diarrhea. Chronic PVT can show signs of portal hypertension, such as ascites, splenomegaly, portal cavernoma, or portal cholangiopathy.[9] In half of cirrhotic patients with SVT, the thrombosis is asymptomatic and diagnosed incidentally at abdominal imaging.[7]

The impact of PVT on the survival of cirrhotic patients is uncertain. Although the mortality associated with PVT has declined in recent years,[10] inpatients with decompensated cirrhosis and PVT showed higher rates of portal hypertension–related complications (such as acute kidney injury and hepatorenal syndrome) and mortality compared to those without PVT.[10] A recent meta-analysis suggested that PVT might worsen the short-term prognosis of cirrhotic patients, being associated with higher risk of hepatic decompensation and higher mortality rate at 1-year follow-up, while it did not seem to influence the long-term prognosis.[11]

Indications to anticoagulant treatment

Most of the management studies involving cirrhotic patients with SVT are small and insufficiently powered to provide definitive conclusions. Previous studies reported that patients with liver cirrhosis are less likely to be treated,[12] showing a variable proportion of cirrhotic patients with SVT receiving anticoagulation (39%-62%).[7,13,14] Results of a systematic review and meta-analysis of 26 studies demonstrated that anticoagulated cirrhotic patients with SVT had lower rates of mortality (9.1% vs 21.0%; relative risk [RR], 0.42 [95% CI, 0.24-0.73]), thrombosis extension (7.1% vs 24.3%; RR, 0.28 [95% CI, 0.15-0.52]) and major bleeding overall (6.4% vs 11.2%; RR, 0.52 [95% CI 0.28-0.97]), compared to nonanticoagulated patients.[15] Regarding the site of bleeding, Loffredo et al reported that variceal bleeding of any severity occurred less frequently in anticoagulated cirrhotic patients (odds ratio [OR], 0.23 [95% CI, 0.06-0.94]).[16] The IMPORTAL individual patient data meta-analysis involving 500 cirrhotic patients with PVT suggested that bleeding not related to portal hypertension might be higher in anticoagulated patients compared to nonanticoagulated patients (9.7% vs 1.7% respectively, $P<0.001$).[17]

In addition, these meta-analyses reported that anticoagulation was associated with recanalization rates approximately 3 time higher than those for no treatment.[15-17] Several studies reported a correlation between vessel recanalization and cirrhosis prognosis, including lower rates of liver-related complications (such as variceal bleeding, ascites, and hepatic encephalopathy)[18]; improvement of the hepatic function, as expressed by the model for end-stage liver disease (MELD) score[19]; and higher transplant-free survival.[20] Conversely, in a retrospective cohort study of 269 untreated cirrhotic patients with SVT, 40% developed the composite outcome of SVT progression, cavernous transformation, intestinal ischemia, portal cholangiopathy, or new arterial or venous thrombotic events.[21]

There is consensus in recent international guidelines (Table 1) that cirrhotic patients with acute SVT should receive anticoagulant treatment[22-25] if it is not contraindicated by active bleeding associated with hemodynamic impairment or by excessively high bleeding risk (for instance, low platelet count, hepatic encephalopathy at risk of falls). However, some guidelines suggest also considering the precise location (main trunk vs branches of the portal vein) and the degree of occlusion (<50% vs >50% of the lumen).[6,22,24]

For patients with chronic SVT (defined by the presence of portal cavernoma or persistent thrombosis), a case-by-case approach has been suggested.[22-24] Since it is difficult to date a chronic SVT and to decide whether anticoagulation is required, other clinical elements might support the choice of anticoagulation in these patients, such as the presence of major inherited thrombophilia, thrombus progression, and history of mesenteric vein thrombosis with bowel ischemia.[22] The benefit of anticoagulation in chronic SVT is less evident.[6] Ai et al enrolled 80 cirrhotic patients with chronic PVT, of whom 40 received oral anticoagulant treatment (with either rivaroxaban or dabigatran) and 40 constituted the nonanticoagulated control group.[26] Anticoagulation resulted in only 12.8% recanalization rates at the 3-month follow-up and 28.2% recanalization rates at the 6-month follow-up.[26] Zhou et al evaluated 84 cirrhotic patients with portal cavernoma, of whom 46 received warfarin.[27] Despite the limited benefit of anticoagulation on recanalization rates (17.4% at a median follow-up of 51 months), anticoagulated patients showed less hepatic decompensation (13.0% vs 34.2%, $P=0.021$) compared to nonanticoagulated patients.[27]

Timing of anticoagulant treatment

Early anticoagulation in SVT increases the chances of achieving vessel recanalization[28] and is recommended by international guidelines[6,23] (Table 1); however, the actual timing of anticoagulant treatment in cirrhotic patients remains unclear. For instance, Delgado et al. enrolled 55 cirrhotic patients with PVT treated with low-molecular-weight heparin (LMWH) or vitamin K antagonist (VKA); of those patients, 35 started anticoagulation within 14 days and 20 started >14 days after diagnosis.[18] Early anticoagulation resulted in higher recanalization rates compared to late anticoagulation (71% vs 40%, $P=0.044$).[18] Rodriguez-Castro et al evaluated 65 cirrhotic patients with PVT on LMWH treatment; 45 of those patients were treated within 6 months; 11, between 7 and 12 months; and 9, after 12 months from the estimated thrombus onset.[29] Recanalization occurred in 76%, 55% and 33%, respectively ($P<0.001$). The time interval between thrombus onset and start of anticoagulant treatment, the severity of liver disease (Child-Pugh class), and the degree of PVT occlusion (partial vs complete) were included by the authors in a model to predict the success of anticoagulation in cirrhotic PVT.[29]

Choice of anticoagulant drug

The standard treatment of SVT in patients with liver cirrhosis consists of LMWH for initial treatment, eventually followed by

Table 1. Recent guidelines on the treatment of splanchnic vein thrombosis in cirrhotic patients

Guideline (year)	Indication	Timing	Drug	Duration
AASLD (2020)[6]	• Anticoagulation is essential in recent PVT and concern for intestinal ischemia • In cirrhotic patients with PVT without ischemic symptoms, consider treatment on a case-by-case basis • Cirrhotic patients with recent thrombosis of small intrahepatic subbranches of PV or minimally occlusive thrombosis of the main PV (<50% lumen): observation with serial imaging is reasonable; anticoagulant treatment if clot progression • Cirrhotic patients with recent occlusive or partially occlusive thrombosis of the main PV (>50% lumen): antithrombotic therapy should be considered	• Anticoagulation should be initiated as soon as possible (not delayed until variceal eradication or adequate beta-blockade is achieved)	• Choice of anticoagulant drug (LMWH, VKA, DOAC) should be individualized, in consultation with a hematologist and/or hepatologist • Limited data on DOAC, use with caution in cirrhotic patients with advanced portal hypertension	Not mentioned
ACG (2020)[22]	• Anticoagulation recommended for: ◦ acute complete main PVT ◦ MVT ◦ PVT extension into MV • Risk of bleeding must be weighted against benefits (eg, low platelet counts <50×10^9/L, or hepatic encephalopathy at risk of falls)	• Initiation of anticoagulation delayed if active bleeding	• Initial treatment with UFH or LMWH • UFH preferred if renal insufficiency • LMWH preferred if thrombocytopenia • Maintenance with oral anticoagulants or LMWH • Limited experience with DOAC	• 6 months for cirrhotic patients with acute PVT or MVT • Continue beyond 6 months in patients on the waiting list for liver transplant
ISTH (2020)[23]	• Anticoagulation recommended for cirrhotic patients with SVT, if no active bleeding or other contraindications	• Early anticoagulant treatment	• Start with therapeutic dose LMWH • Switch to VKA or DOAC, if not contraindicated by severe liver dysfunction • Reduced doses of LMWH or DOAC may be used for longer/indefinite duration	• At least 3–6 months • Longer or indefinite duration if: ◦ thrombosis progression ◦ recurrence after anticoagulant discontinuation ◦ unprovoked SVT ◦ persistent risk factors
AGA (2021)[25]	• Anticoagulation suggested for cirrhotic patients with acute or subacute nontumoral PVT	Not mentioned	• No data to support the use of 1 anticoagulant over another	Not mentioned
Baveno VII (2022)[24]	• Anticoagulation recommended in cirrhotic patients with: ◦ recent complete or partial occlusion (>50%) of the PV trunk ◦ symptomatic PVT ◦ PVT in candidates for liver transplant • Anticoagulation should be considered in cirrhotic patients with minimally occlusive (<50%) thrombosis of the PV trunk if: ◦ thrombus progression at 1–3 months follow-up ◦ involvement of superior MV • Case-by-case basis if low platelet count (<50×10^9/L)	Not mentioned	• Initial treatment with LMWH • Maintenance with LMWH, VKA, DOAC • Monitoring VKA can be challenging in cirrhotic patients • Regarding DOAC: ◦ no major safety concern with Child-Pugh A; ◦ use with caution in Child-Pugh B for possible accumulation; ◦ not recommended in Child-Pugh C	• Anticoagulation should be: ◦ maintained for at least 6 months and until PV recanalization; ◦ continued after recanalization in candidates for liver transplant; ◦ considered after recanalization in all patients, balancing risks and benefits

AASLD, American Association for the Study of Liver Diseases; ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; DOAC, direct oral anticoagulant; INR, international normalized ratio; ISTH, International Society on Thrombosis and Haemostasis; LMWH, low-molecular-weight heparin; MV, mesenteric vein; MVT, mesenteric vein thrombosis; PV, portal vein; PVT, portal vein thrombosis; SVT, splanchnic vein thrombosis; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

oral anticoagulant drugs. LMWH is a versatile drug which allows dose-reductions (eg, in case of severe thrombocytopenia [see paragraph 8] or severe renal insufficiency).[30] However, anti-Xa monitoring is not recommended in liver cirrhosis because the reduced antithrombin levels found in cirrhotic patients are associated with decreased baseline anti-Xa levels.[31] Regarding the dose regimen, Cui et al enrolled 65 cirrhotic patients with PVT and randomized them to enoxaparin 1 mg/kg twice daily (BID) or 1.5 mg/kg once daily (OD).[32] Recanalization (partial or complete) occurred in 80.6% vs 76.5%, respectively ($P = 0.67$); there were no episodes of variceal bleeding, and nonvariceal bleeding was significantly lower in the BID dose group (6.5% vs 23.5%; $P = 0.048$).[32]

Unfractionated heparin (UFH) can be considered in the presence of severe renal failure (estimated glomerular filtration rate <30 mL/min) or in patients who might need invasive procedures. However, it is usually not recommended for cirrhotic patients because of difficulties in monitoring (since the baseline activated partial thromboplastin time can be prolonged in liver cirrhosis) and because of the risk of heparin-induced thrombocytopenia, which might contribute to the cirrhosis-related thrombocytopenia.[24]

Oral anticoagulants, such as VKAs or direct oral anticoagulants (DOACs) can be considered for maintenance and long-term treatment. However, monitoring VKA may be difficult in patients with baseline prolongation of the international normalized ratio (INR).[30] Although DOACs are considered off-label in several countries, there is increasing evidence on their use in noncirrhotic patients, in whom they showed a favorable safety and efficacy profile.[33-35] There are only a few studies specifically evaluating the treatment of cirrhotic SVT,[14,26,36] and they are summarized in Table 2. Nonetheless, cirrhotic patients tend to receive reduced doses of the DOACs in real life clinical practice,[37] and the DOACs are contraindicated in patients with Child-Pugh class C (and rivaroxaban is contraindicated also in Child-Pugh B). A recent systematic review and metanalysis comparing DOACs with VKAs in cirrhotic PVT found that the DOACs had higher recanalization rates (RR, 1.67 [95% CI, 1.02-2.74]) and lower rates of PVT progression (RR 0.14, 95%CI 0.03-0.57).[38] However, these results should be interpreted with caution because most of the included studies were small retrospective observational studies with substandard quality of anticoagulation control in the VKA group.

The safety profile of the DOACs in patients with liver disease has been recently investigated by Lawal et al, who described >10 000 patients with atrial fibrillation and chronic liver disease, including 29% with liver cirrhosis.[39] The incidence rates of hospitalizations for major bleeding were lower in the DOAC than in the VKA group (7.9 vs 15.0 per 100 patient-years; hazard ratio [HR], 0.69 [95% CI, 0.58-0.82]). When analyzing the different DOACs separately, rivaroxaban was associated with higher rates of major bleeding than apixaban (9.1 vs 6.5 per 100 patient-years; HR, 1.59 [95% CI, 1.18-2.14]).[39] In addition, different anticoagulants showed different patterns of bleeding events. In a large study based on the World Health Organization pharmacovigilance database, which includes all reported bleeding in unselected adult patients, Montastruc et al found that when compared to VKAs, DOACs were associated with less cerebral, urological, and nasal bleeding but more gynecological bleeding (adjusted reporting OR, 3.75 [95% CI, 3.41-4.13]).[40] Furthermore, anti-Xa inhibitors were associated with less digestive bleeding (adjusted reporting OR, 0.78 [95% CI, 0.75-0.80]), but more bleeding in other locations compared to direct thrombin inhibitors.[40]

Duration of anticoagulant treatment

Patients with SVT should be treated for at least 3-6 months,[22,23] and a longer treatment duration should be considered for patients with liver cirrhosis, because liver cirrhosis is a persistent risk factor for recurrent thrombosis (Table 1). The Baveno VII consensus suggests to treat cirrhotic patients for at least 6 months or until portal vein recanalization is achieved and to carefully balance risks and benefits when considering prolonged treatment.[24] In a study evaluating 90 patients with SVT after discontinuation of VKA treatment, the rates of thrombotic events in cirrhotic patients were 19.1 per 100 patient-years, and liver cirrhosis emerged as a strong independent risk factor (HR, 7.9 [95% CI, 1.8-35.9]).[41] Furthermore, high rates of PVT extension or recurrence after discontinuing anticoagulation were reported in the study by Pettinari et al, in which 182 cirrhotic patients with PVT were enrolled (36% in patients with partial/complete recanalization, 20% in patients without any sign of recanalization).[13]

Although cirrhotic SVT carries a higher risk of bleeding than noncirrhotic SVT,[3] a recent meta-analysis highlighted that anticoagulant therapy did not further increase the hemorrhagic risk in cirrhotic patients but was actually associated with lower rates of major bleeding events compared to no anticoagulant treatment.[15] This finding can potentially be explained by the higher rates of vessel recanalization,[15] which may prevent portal hypertension–related bleeding. Despite the lack of specific studies on SVT, the guidelines from the International Society on Thrombosis and Haemostasis suggested that reduced doses of LMWH or DOAC be considered for the extended treatment of SVT in order to minimize the risk of bleeding events,[23] as recommended for patients with deep vein thrombosis of the lower extremities or pulmonary embolism.[42] The use of reduced doses of DOACs is also supported by a recently published study that evaluated rivaroxaban 15mg OD vs no anticoagulation for secondary prevention of SVT in noncirrhotic patients.[35]

Long-term anticoagulation is recommended for cirrhotic patients who are candidates for liver transplantation[22,24]; the aim is to prevent SVT progression and to recanalize the portal and superior mesenteric veins, which will simplify vessel anastomosis and improve posttransplant outcomes.[43] In the study by Bert et al, PVT was detected in around 10% of patients on the waiting list for liver transplantation and was associated with more complex surgical procedures and reduced 1-year survival.[44] Of note, despite abdominal imaging screening while patients were on the waiting list, in more than 50% of cases, PVT was diagnosed intraoperatively.[44] The duration of anticoagulation after liver transplantation is still debated. A short course of anticoagulation is recommended to prevent early rethrombosis, which can lead to graft loss, while the need for longer anticoagulation should be evaluated on a case-by-case basis, considering also the type of anastomosis performed and the presence of underlying prothrombotic states.[45]

Anticoagulation and gastroesophageal varices

Gastroesophageal varices do not represent a contraindication to anticoagulant treatment, as long as adequately prophylaxis is provided.[22,23] For primary prophylaxis of variceal bleeding, guidelines recommend nonselective beta-blockers,

Table 2. Studies evaluating the direct oral anticoagulants for the treatment of splanchnic vein thrombosis in patients with liver cirrhosis

Authors (year)	Study design	Patient characteristics	Treatment duration	No. of patients	Treatment	Recanalization (partial or complete)	SVT progression or recurrence	Bleeding events
Nagaoki et al. (2018)[36]	Retrospective	50 cirrhotic patients with PVT: • CP A n=29 • CP B n=16 • CP C n=5	6 months	20	Danaparoid sodium 2500 U/day for 2 weeks ⟶ Edoxaban 30–60 mg	18 (90%)	1 (5%)	Clinically significant GI bleeds: 3 (15%)
				30	Danaparoid sodium 2500 U/day for 2 weeks ⟶ Warfarin (INR target range 1.5–2.0)	9 (30%)	14 (47%)	Clinically significant GI bleeds: 2 (7%)
Ai et al. (2020)[26]	Prospective	80 cirrhotic patients with chronic PVT (all CP classes were enrolled)	6 months	40	DOACs: • Rivaroxaban 20 mg OD • Dabigatran 150 mg BID	11 (28%)	3 (8%)	Any bleed: 3 (8%)
				40	No anticoagulant treatment	1 (3%)	4 (11%)	Any bleed: 1 (3%)
Naymagon et al. (2021)[14]	Retrospective	214 cirrhotic patients with acute PVT: • CP A n=52 • CP B n=99 • CP C n=63	19 months (median)	42	Enoxaparin 1 mg/kg BID	16 (38%)*	8 (19%)	Major bleed: 9 (21%)
				26	Warfarin (INR target range 2.0–3.0)	15 (58%)*	4 (15%)	Major bleed: 5 (19%)
				18	DOACs: • Apixaban 10 mg BID for 7 days ⟶5 mg BID • Rivaroxaban 15 mg BID for 21 days ⟶20 mg OD • Dabigatran 150 mg BID	10 (56%)*	1 (6%)	Major bleed: 3 (17%)
				128	No anticoagulant treatment	34 (27%)*	33 (26%)	Major bleed: 22 (17%)

* Includes complete recanalization only.

BID, twice daily; CP, Child-Pugh class; DOACs, direct oral anticoagulants; GI, gastrointestinal; INR, international normalized ratio; NR, not reported; OD, once daily; PVT, portal vein thrombosis; SVT, splanchnic vein thrombosis; ⟶, then.

such as carvedilol (which has also alpha-adrenergic vasodilatory effect), propranolol, or nadolol. Prevention of a first variceal bleeding is crucial in cirrhotic patients, since variceal bleeding is one of the characteristics that define hepatic decompensation.[24] Endoscopic variceal band ligation (EVL) is recommended for primary prophylaxis if beta-blockers are contraindicated or not tolerated and for the treatment of acute variceal bleeding.[24]

Timing of anticoagulation in patients with gastroesophageal varices is unclear. The 2020 guidelines of the American Association for the Study of Liver Diseases suggest to start anticoagulation early, without the need to wait for varices eradication or complete beta-blockade.[6] In addition, they state that EVL can be performed without the need to stop anticoagulant therapy.[6]

In a randomized controlled trial by Gao et al, 86 cirrhotic patients with PVT and acute variceal bleeding within 48 hours after EVL were randomly allocated to anticoagulation (nadroparin 1 mg/kg for 1 month, followed by warfarin with INR target range 2.0-3.0 for 5 months) or no anticoagulant therapy.[46] Endoscopic variceal band ligation was performed monthly (discontinuing anticoagulation 3 days before) until varices eradication, and all patients received carvedilol. As expected, portal vein recanalization was significantly higher in the treated group (67.4% vs 39.5%, $P = 0.009$). Of note, there were no recurrent variceal bleedings at 5-day and 14-day follow-ups, and the rates were similar in the 2 groups at 4-week (2.3% vs. 4.7%, $P = 0.99$), 6-week (4.7% vs. 9.3%, $P = 0.67$) and 6-month (18.6% vs. 20.9%, $P = 0.78$) follow-ups.[46] Bianchini et al evaluated 265 cirrhotic patients undergoing 553 EVL procedures, of which 169 were performed during treatment with LMWH and 384 were performed without any anticoagulant treatment.[47] Rates of bleeding were similar in the 2 groups (3.8% vs 1.6%, $P = 0.29$).[47]

Anticoagulation in thrombocytopenia

Thrombocytopenia (defined as platelet count $<150 \times 10^9$/L) is found in approximately 76% of cirrhotic patients.[48] Mild thrombocytopenia (>75 to $<150 \times 10^9$/L) is the most common, while moderate (50 to 75×10^9/L) and severe ($<50 \times 10^9$/L) thrombocytopenia were reported in 13% and 1% of patients with liver cirrhosis, respectively.[48] More recently, Basili et al reported the presence of severe thrombocytopenia in ~8% of cirrhotic patients.[49] In patients with liver cirrhosis, low platelet count is not predictive of the overall bleeding risk[49] but is a marker of the severity of portal hypertension. In fact, low platelet count has been reported to predict the development of PVT.[5]

There are no guidelines specifically addressing the management of anticoagulation in cirrhosis-associated thrombocytopenia. In patients with mild to moderate thrombocytopenia, the risk of spontaneous bleeding is low,[50] and full-dose anticoagulation was reported to be safe.[51] Thus, the guidance from International Society on Thrombosis and Haemostasis on the management of cancer-associated thrombosis in patients with thrombocytopenia recommends full-therapeutic dose anticoagulation if platelet count $\geq 50 \times 10^9$/L.[51]

For patients with severe thrombocytopenia, the bleeding risk associated with anticoagulation should be balanced against the risk of thrombus progression (eg, onset and extension of SVT). Intermediate or prophylactic dose of LMWH can be considered if the platelet count is $25\text{-}50 \times 10^9$/L, and temporarily discontinuation if platelet count $<25 \times 10^9$/L.[51] There are limited data on the use of DOACs in severe thrombocytopenia; thus, they are not recommended in this setting.[51]

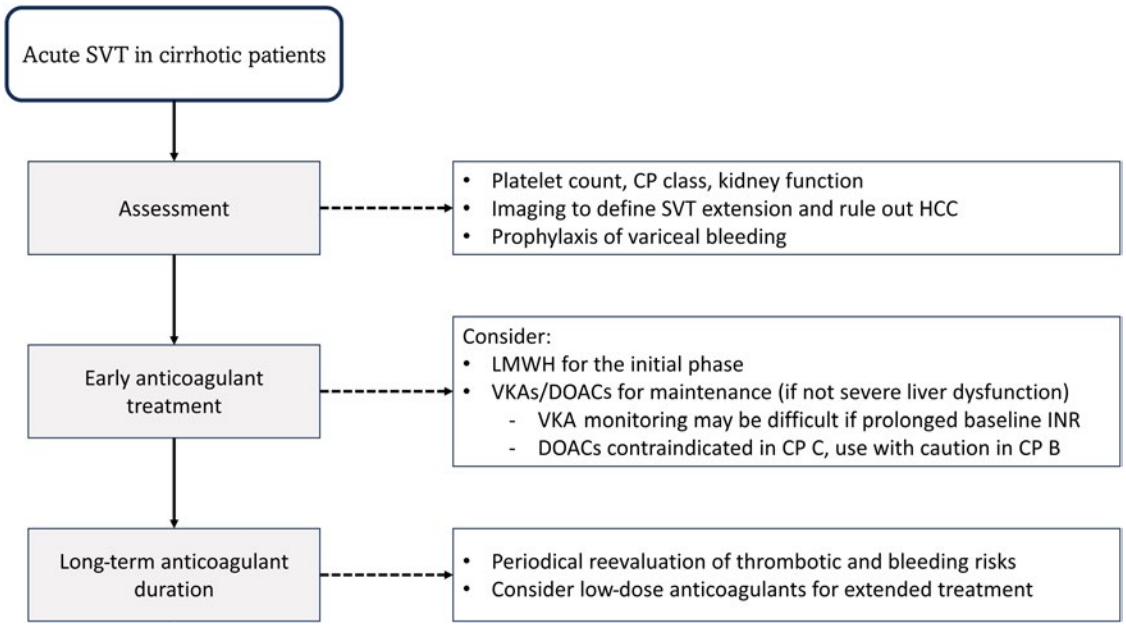

Figure 1. Proposed treatment algorithm for cirrhotic patients with acute splanchnic vein thrombosis. CP, Child-Pugh; DOACs, direct oral anticoagulants; HCC, hepatocellular carcinoma; INR, international normalized ratio; LMWH, low-molecular-weight heparin; SVT, splanchnic vein thrombosis; VKAs, vitamin K antagonists.

CLINICAL CASE (continued)

After a few days of enoxaparin 1 mg/kg twice daily, given clinical stability, the patient was switched to rivaroxaban at standard therapeutic dose (15 mg twice daily for 3 weeks, followed by 20 mg once daily). A computed tomography scan performed at the 6-month follow-up showed a patent portal vein, without any signs of cavernoma. Continuation of long-term anticoagulant treatment was indicated given the underlying presence of liver cirrhosis, and the possibility of a low-dose DOAC (eg, rivaroxaban 10 mg OD or apixaban 2.5 mg BID) was considered.

Conclusion

Cirrhotic patients with acute SVT should receive anticoagulant treatment unless major contraindications exist. Starting anticoagulation early, along with adequate prophylaxis of variceal bleeding, increases the rates of vessel recanalization and improves the prognosis. Anticoagulation should be prescribed long-term; however, it might need to be adjusted based on comorbidities (such as low platelet count and liver impairment). Our proposed management of cirrhotic SVT is summarized in the Figure 1.

Conflict-of-interest disclosure

Nicoletta Riva has no relevant conflicts to declare in relation to this paper.

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Off-label drug use

The use of direct oral anticoagulants for splanchnic vein thrombosis is off-label in several countries.

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References

1. Caiano LM, Riva N, Ageno W. Anticoagulant therapy for splanchnic vein thrombosis: recent updates for patients with liver cirrhosis. *Expert Rev Hematol.* 2023;16(2):121-129.
2. Pan J, Wang L, Gao F, et al. Epidemiology of portal vein thrombosis in liver cirrhosis: a systematic review and meta-analysis. *Eur J Intern Med.* 2022;104:21-32.
3. Ageno W, Riva N, Schulman S, et al. Long-term clinical outcomes of splanchnic vein thrombosis: results of an international registry. *JAMA Intern Med.* 2015;175(9):1474-1480.
4. 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.
5. Turon F, Driever EG, Baiges A, et al. Predicting portal thrombosis in cirrhosis: a prospective study of clinical, ultrasonographic and hemostatic factors. *J Hepatol.* 2021;75(6):1367-1376.
6. Northup PG, Garcia-Pagan JC, Garcia-Tsao G, et al. Vascular liver disorders, portal vein thrombosis, and procedural bleeding in patients with liver disease: 2020 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology.* 2021;73(1):366-413.
7. Senzolo M, Riva N, Dentali F, et al; IRSVT study investigators. Long-term outcome of splanchnic vein thrombosis in cirrhosis. *Clin Transl Gastroenterol.* 2018;9(8):176.
8. Miñano C, Garcia-Tsao G. Clinical pharmacology of portal hypertension. *Gastroenterol Clin North Am.* 2010;39(3):681-695.
9. Adams L, Ball S. Diagnosis and management of portal vein thrombosis in patients with cirrhosis of liver. *Southwest Resp Crit Care Chronicles.* 2018;6(26):1-7.
10. Cool J, Rosenblatt R, Kumar S, et al. Portal vein thrombosis prevalence and associated mortality in cirrhosis in a nationally representative inpatient cohort. *J Gastroenterol Hepatol.* 2019;34(6):1088-1092.
11. Xian J, Tang Y, Shao H, Wang X, Zhang M, Xing T. Effect of portal vein thrombosis on the prognosis of patients with cirrhosis without a liver transplant: a systematic review and meta-analysis. *Medicine (Baltimore).* 2021;100(16):e25439.
12. Candeloro M, Valeriani E, Monreal M, et al. Anticoagulant therapy for splanchnic vein thrombosis: an individual patient data meta-analysis. *Blood Adv.* 2022;6(15):4516-4523.
13. Pettinari I, Vukotic R, Stefanescu H, et al; BO-LIVES (BOlogna LIVEr vascular Studies). Clinical impact and safety of anticoagulants for portal vein thrombosis in cirrhosis. *Am J Gastroenterol.* 2019;114(2):258-266.
14. Naymagon L, Tremblay D, Zubizarreta N, Moshier E, Mascarenhas J, Schiano T. Safety, efficacy, and long-term outcomes of anticoagulation in cirrhotic portal vein thrombosis. *Dig Dis Sci.* 2021;66(10):3619-3629.
15. Valeriani E, Di Nisio M, Riva N, et al. Anticoagulant treatment for splanchnic vein thrombosis in liver cirrhosis: a systematic review and meta-analysis. *Thromb Haemost.* 2021;121(7):867-876.
16. Loffredo L, Pastori D, Farcomeni A, Violi F. Effects of anticoagulants in patients with cirrhosis and portal vein thrombosis: a systematic review and meta-analysis. *Gastroenterology.* 2017;153(2):480-487.e1487e1.
17. Guerrero A, Campo LD, Piscaglia F, et al; Baveno Cooperation: an EASL consortium. Anticoagulation improves survival in patients with cirrhosis and portal vein thrombosis: the IMPORTAL competing-risk meta-analysis. *J Hepatol.* 2023;79(1):69-78.
18. Delgado MG, Seijo S, Yepes I, et al. Efficacy and safety of anticoagulation on patients with cirrhosis and portal vein thrombosis. *Clin Gastroenterol Hepatol.* 2012;10(7):776-783.
19. Rupoli S, Fiorentini A, Morsia E, et al. Anticoagulation and vessel recanalization in cirrhotic patients with splanchnic vein thrombosis: a multidisciplinary "real life" experience. *Vasc Health Risk Manag.* 2021;17:619-629.
20. La Mura V, Braham S, Tosetti G, et al. Harmful and beneficial effects of anticoagulants in patients with cirrhosis and portal vein thrombosis. *Clin Gastroenterol Hepatol.* 2018;16(7):1146-1152.e41152e4.
21. McMurry H, Sabile JMG, Elstrott B, et al. Clinical predictors for thrombus progression in cirrhotic patients with untreated splanchnic vein thrombosis. *Thromb Res.* 2022;216:1-7.
22. Simonetto DA, Singal AK, Garcia-Tsao G, Caldwell SH, Ahn J, Kamath PS. ACG Clinical Guideline: disorders of the hepatic and mesenteric circulation. *Am J Gastroenterol.* 2020;115(1):18-40.
23. Di Nisio M, Valeriani E, Riva N, Schulman S, Beyer-Westendorf J, Ageno W. Anticoagulant therapy for splanchnic vein thrombosis: ISTH SSC Subcommittee Control of Anticoagulation. *J Thromb Haemost.* 2020;18(7):1562-1568.
24. de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C; Baveno VII Faculty. Baveno VII - Renewing consensus in portal hypertension. *J Hepatol.* 2022;76(4):959-974.
25. O'Shea RS, Davitkov P, Ko CW, et al. AGA clinical practice guideline on the management of coagulation disorders in patients with cirrhosis. *Gastroenterology.* 2021;161(5):1615-1627.e11627e1.
26. Ai M-H, Dong W-G, Tan X-P, et al. Efficacy and safety study of direct-acting oral anticoagulants for the treatment of chronic portal vein thrombosis in patients with liver cirrhosis. *Eur J Gastroenterol Hepatol.* 2020;32(10):1395-1400.
27. Zhou Y, Zhuang Z, Yu T, et al. Long-term efficacy and safety of anticoagulant for cavernous transformation of the portal vein cirrhotic patient with extrahepatic portal vein obstruction. *Thromb J.* 2023;21(1):6.
28. Wang L, Guo X, Xu X, et al. Anticoagulation favors thrombus recanalization and survival in patients with liver cirrhosis and portal vein thrombosis: results of a meta-analysis. *Adv Ther.* 2021;38(1):495-520.
29. Rodriguez-Castro KI, Vitale A, Fadin M, et al. A prediction model for successful anticoagulation in cirrhotic portal vein thrombosis. *Eur J Gastroenterol Hepatol.* 2019;31(1):34-42.
30. Senzolo M, Garcia-Tsao G, García-Pagán JC. Current knowledge and management of portal vein thrombosis in cirrhosis. *J Hepatol.* 2021;75(2):442-453.

31. Ha NB, Regal RE. Anticoagulation in patients with cirrhosis: caught between a rock-liver and a hard place. *Ann Pharmacother.* 2016;50(5):402-409.
32. Cui S-B, Shu R-H, Yan S-P, et al. Efficacy and safety of anticoagulation therapy with different doses of enoxaparin for portal vein thrombosis in cirrhotic patients with hepatitis B. *Eur J Gastroenterol Hepatol.* 2015;27(8):914-919.
33. Ageno W, Beyer Westendorf J, Contino L, et al. Rivaroxaban for the treatment of non-cirrhotic splanchnic vein thrombosis: an interventional prospective cohort study. *Blood Adv.* 2022;6(12):3569-3578.
34. Naymagon L, Tremblay D, Zubizarreta N, et al. The efficacy and safety of direct oral anticoagulants in noncirrhotic portal vein thrombosis. *Blood Adv.* 2020;4(4):655-666.
35. Plessier A, Goria O, Cervoni JP, et al. Rivaroxaban prophylaxis in noncirrhotic portal vein thrombosis. *NEJM Evid.* 2022;1(12).
36. Nagaoki Y, Aikata H, Daijyo K, et al. Efficacy and safety of edoxaban for treatment of portal vein thrombosis following danaparoid sodium in patients with liver cirrhosis. *Hepatol Res.* 2018;48(1):51-58.
37. De Gottardi A, Trebicka J, Klinger C, et al; VALDIG Investigators. Antithrombotic treatment with direct-acting oral anticoagulants in patients with splanchnic vein thrombosis and cirrhosis. *Liver Int.* 2017;37(5):694-699.
38. Koh JH, Liew ZH, Ng GK, et al. Efficacy and safety of direct oral anticoagulants versus vitamin K antagonist for portal vein thrombosis in cirrhosis: a systematic review and meta-analysis. *Dig Liver Dis.* 2022;54(1):56-62.
39. Lawal OD, Aronow HD, Shobayo F, et al. Comparative effectiveness and safety of direct oral anticoagulants and warfarin in patients with atrial fibrillation and chronic liver disease: a Nationwide Cohort Study. *Circulation.* 2023;147(10):782-794.
40. Montastruc J-L, Tessier S, Bura-Riviere A. Differences in the location of bleeding with direct oral anticoagulants vs. vitamin K antagonists: a study in the World Health Organization's pharmacovigilance database. *Br J Clin Pharmacol.* 2023;89(7):2201-2207.
41. Riva N, Ageno W, Poli D, et al. 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.
42. Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report. *Chest.* 2021;160(6):e545-e608.
43. Biolato M, Paratore M, Di Gialleonardo L, Marrone G, Grieco A. Direct oral anticoagulant administration in cirrhotic patients with portal vein thrombosis: what is the evidence? *World J Hepatol.* 2022;14(4):682-695.
44. Bert J, Geerts A, Vanlander A, et al. Up to 50% of portal vein thrombosis remains undiagnosed until liver transplantation. *Clin Transplant.* 2020;34(12):e14107.
45. Francoz C, Valla D, Durand F. Portal vein thrombosis, cirrhosis, and liver transplantation. *J Hepatol.* 2012;57(1):203-212.
46. Gao Z, Li S, Zhao J, Li J, Gao Y. Anticoagulation therapy early is safe in portal vein thrombosis patients with acute variceal bleeding: a multi-centric randomized controlled trial. *Intern Emerg Med.* 2023;18(2):513-521.
47. Bianchini M, Cavani G, Bonaccorso A, et al. Low molecular weight heparin does not increase bleeding and mortality post-endoscopic variceal band ligation in cirrhotic patients. *Liver Int.* 2018;38(7):1253-1262.
48. Afdhal N, McHutchison J, Brown R, et al. Thrombocytopenia associated with chronic liver disease. *J Hepatol.* 2008;48(6):1000-1007.
49. Basili S, Raparelli V, Napoleone L, et al; PRO-LIVER Collaborators. Platelet count does not predict bleeding in cirrhotic patients: results from the PRO-LIVER Study. *Am J Gastroenterol.* 2018;113(3):368-375.
50. Peck-Radosavljevic M. Thrombocytopenia in chronic liver disease. *Liver Int.* 2017;37(6):778-793.
51. Samuelson Bannow BT, Lee A, Khorana AA, et al. Management of cancer-associated thrombosis in patients with thrombocytopenia: guidance from the SSC of the ISTH. *J Thromb Haemost.* 2018;16(6):1246-1249.

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