Review Article

Update on Management of Portal Vein Thrombosis and the Role of Novel Anticoagulants

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Abstract

The clinical management of portal vein thrombosis (PVT) remains ambiguous due to its heterogeneous presentations and its associations with liver disease, malignancy, and hypercoagulable states. The natural history and clinical outcome of PVT are highly variable, dependent upon size, extent and degree of the thrombotic occlusion, as well as the physiological impact of patient comorbidities. While existing clinical guidelines consistently recommend low molecular weight heparin or vitamin K antagonist anticoagulation in cirrhotic patients with symptomatic acute PVT, management of asymptomatic and chronic PVT may need to be determined on a case-by-case basis, factoring in the state of underlying liver disease. In general, patients with PVT and underlying malignancy should be anticoagulated to alleviate symptoms and prevent recurrences that could disrupt the cancer management. However, existing clinical data does not support routine anticoagulation of cirrhotic patients with asymptomatic PVT in the absence of underlying cancer. While low molecular weight heparin and vitamin K antagonist remain the most commonly used agents in PVT, an emerging body of clinical evidence now suggests that direct-acting oral anticoagulants may be used safely and effectively in PVT. As such, direct-acting oral anticoagulants may offer a more convenient anticoagulation alternative for PVT management in future practice.

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Risk factors and natural history

Since the first description of portal vein thrombosis (PVT) by Balfour and Stewart in 1869, in their report of a 20-year-old patient who died from complications of splenomegaly, ascites, and varicose dilation with associated PVT, the clinical manifestations and management of PVT have been met with great interest.¹ PVT is classically defined as obstruction of the portal vein by thrombus, graded based upon the extent of vascular occlusion.² As an entity, it has been included occasionally in splanchnic vein thrombosis (SPVT), referring to the thrombotic involvement of portal, mesenteric, splenic veins, and in Budd-Chiari syndrome, based on shared etiology and risk factors.³⁻⁵

The incidence rate of PVT is unknown. The population prevalence has been reported as 1% based on an autopsy series from Sweden⁶ and has been proposed to range between 0.6% to 26% in patients with liver cirrhosis,⁷⁻⁹ in which the incidence of PVT rises with severity of liver disease. In patients undergoing liver transplantation for end-stage liver diseases, for example, studies have reported 5.5% to 26% prevalence.¹⁰

Risk factors of PVT adhere to Virchow’s triad of thrombus formation: stasis of blood flow, endothelial injury, and hypercoagulability (Table 1).¹¹⁻¹² In addition to cirrhosis, PVT is common with hepatobiliary cancers.¹³ For hepatocellular cancer (HCC), 23% and 44% of untreated and autopsy series of patients were found to have PVT, respectively.¹⁴,¹⁵ HCC alone confers >100-fold risk of PVT over that for the general population. In the absence of associated cirrhosis or malignancy, myeloproliferative neoplasms (MPNs) have been shown to be the most common underlying prothrombotic factor for acute PVT. In a meta-analysis of 32 studies assessing the prevalence of MPNs in PVT patients, MPNs were present in 166 out of 855 (31.5%) cases. Of these patients with MPN, 86.6% were found to have the JAK2V617F mutation.¹⁶ Thrombophilias (deficiency of antithrombin-III, protein C or protein S, and factor V Leiden mutation) are known risk factors for venous thromboembolism (VTE).¹⁷ These account for less than 10% of all recurrent VTE and confer only a modest increased risk (<5-fold) for PVT (Table 1).

Hypercoagulability leading to a prothrombotic state is the primary pathophysiological factor leading to PVT, underscored by the high incidence of concomitant nonportal vein VTEs.¹⁸ Based on the report of Ögren et al.⁶, up to 70% of patients with noncirrhotic PVT may have underlying malignancy or MPN. Indeed, Sogaard et al.¹⁹ proposed the presence of SPVT as a marker for occult malignancy, as 3-month and 5-year absolute cancer risks were found to be 8.0% and 14.8%, respectively, in patients who presented with SPVT.

The natural history of PVT has not been well described due to the wide variability of underlying causes and patient-specific determinants, such as the associated prothrombotic state and vascular/liver physiology. In patients without underlying malignancy, the clinical course of PVT can vary in the different stages...
of liver disease. In a study population consisting of 40% alcohol users with good baseline liver function, being representative of PVT in the setting of early chronic liver disease, the natural history of PVT was indolent. In 85% of these patients with nonocclusive PVT, 70% showed spontaneous resolution and 19% showed resolution and reappearance with very few patients having received anticoagulation therapy. When PVT developed prior to progression of the liver disease, it was not statistically associated with increased risk of liver disease progression or decompensation.20 In contrast, an earlier series by Amitrano et al.7 in patients with more advanced cirrhosis reported 11.2% PVT incidence and 45% were symptomatic with portal hypertensive bleed, abdominal pain, and/or intestinal infarction. In this series, mesenteric vein involvement was always associated with symptoms. In another retrospective series, bleeding was found to be the main presenting symptom. When taken together, PVT incidence markedly increases with cirrhosis and is significantly associated with symptoms of bleeding, abdominal pain, and intestinal infarction.

In patients with HCC and liver cirrhosis, using ultrasound as a screening methodology, Nery et al.21 found the overall 1-, 3- and 5-year cumulative PVT incidence to be 4.6%, 8.2% and 10.7%, respectively. The natural history of patients with PVT and underlying malignancy has not been described; however, the presence of PVT has been identified as an adverse predictor for survival.14,22

Clinical presentation

A new classification system of PVT, based on the site of thrombosis (portal venous trunk and/or its tributary branches), degree of occlusion, duration and presentation, and associated symptoms, has recently been proposed to delineate this relatively common clinical finding within a heterogenous set of diseases (Table 2).23,24 While adoption of this classification system will help to standardize nomenclature and reduce variation in clinical trials, it does not immediately provide instruction in clinical decision-making for patients with individualized risk factors and disease severities. The decision to intervene in PVT will vary, since the clinical objectives must be individualized for nonmalignant noncirrhotics, nonmalignant cirrhotic patients, patients with hepatoabiliary cancer, and patients with hematologic disorders or solid tumor malignancies.

Usually, PVT presents without apparent symptoms, even in patients with advanced liver disease; however, patients with advanced liver disease are more likely to be symptomatic, especially with acute onset and complete thrombotic occlusion of the portal vein.25 In a prospective study of noncirrhotic patients, Plessier et al.26 reported that 91% presented with abdominal pain and that the majority demonstrated signs of systemic inflammation, fever (53%), and elevated C-reactive protein (84%). Intestinal infarction, which has been reported in up to 28% in another series27 was found in two (2/102) patients requiring surgery. Sepsis due to intraabdominal infection or phlebitis was not specifically addressed in this series but has been frequently reported as an early complication of acute PVT.28,29 Intestinal infarction is the most feared complication of acute PVT and is associated with a 60% mortality risk.30

In patients with cirrhosis, symptoms resulting from acute PVT can be highly variable, likely related to the cumulative effect of venous thrombosis on underlying portal hypertension and liver disease. Ascites and bleeding, or portal hypertensive gastropathy are found in 40-80% of cirrhotics who present Table 1. Risk factors of PVT

| Risk factors                             | Relative risk |
|-----------------------------------------|---------------|
| General population prevalence6          | 1             |
| Nonmalignant cirrhosis7,9,21,101        |               |
| Early cirrhosis                         | 4.2-4.6       |
| Advanced cirrhosis                      | 11.2-16.6     |
| Nonmalignant with cirrhosis with portal hypertension101 | 6.1 |
| Malignancies102                         |               |
| Overall                                 | 5.3           |
| Hepatocellular                          | 124           |
| Cholangiocarcinoma                      | 77            |
| Pancreatic                              | 28            |
| Hematologic disorders16,103             |               |
| Factor V-Leiden                         | 4.8           |
| All thrombophilia                       | 1.2           |
| JAK2V617F-positive MPNs                 | 27.7          |
| All MPNs                                | 31.5          |
| Inflammation102                         |               |
| Autoimmune (ulcerative colitis, Crohn's) | 2.5          |
| Autoimmune deficiency syndrome          | 3.6           |

Table 2. Proposed classification

| Site of PVT – (Type 1, 2a, 2b, 3)         |
|------------------------------------------|
| Type 1: Only trunk                       |
| Type 2: Only branch: 2a, one branch; 2b, both branches |
| Type 3: Trunk and branches               |

Degree of portal venous system occlusion (on imaging/Doppler study)

| O: Occlusive                             |
|------------------------------------------|
| NO: Nonocclusive                         |

Duration and presentation (R, C)

| R: Recent (first time detected in previously patent portal vein, presence of hyperdense thrombus on imaging, absent or limited collateral circulation, dilated portal vein at the site of occlusion) |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| -S: Symptomatic (acute PVT features with or without "ABI") |
| -AS: Asymptomatic                                                                                                                   |
| C: Chronic (no hyperdense thrombus; previously diagnosed PVT on follow-up, portal cavernoma and clinical features of "PHT") |
| -S: Symptomatic (features of "PHT") |
| -AS: Asymptomatic                                                                                                                  |
Intestinal infarction is reported in 2-12% of these patients, correlating with involvement of the mesenteric vein. Hepatic decompensation is found both in high frequency at presentation and as a complication of PVT, and is likely a marker of advanced liver disease. Encephalopathy is also common, occurring in 10-25% of patients.

Chronic PVT occurs when acute PVT fails to resolve, resulting eventually in the formation of collateral vasculature bypassing the area of obstruction (known as cavernous transformation). Cavernous transformation of the portal vein has been shown to occur between 6-12 days from unresolved PVT with bypass of blood through the paracholedochal veins. The location of these cavernomas results in cholestasis in 50-90% of the patients but causes biliary obstruction only in the minority (6-25%) of these cases. However, in a case series of PVT in cirrhotics, Sogaard et al. found that chronic PVT did not differ significantly from acute PVT in clinical presentation; therefore, symptoms classically associated with acute PVT may still herald chronic PVT with incomplete or delayed resolution.

**Evaluation**

Serial screening with Doppler ultrasound has been recently proposed for patients with cirrhosis and portal hypertension, and in candidates on the waiting list for liver transplantation. Asymptomatic PVTs, however, are primarily found incidentally on initial computer tomography (commonly known as CT) or magnetic resonance imaging (commonly known as MRI) of the liver. Clinically suspected PVTs are generally established by conventional and Doppler ultrasound (Fig. 1). Color Doppler studies demonstrate an accuracy of 88-98% with sensitivity/specificity in the 80-100% range, and is considered sufficient for diagnosis (Fig. 2).

Contrast-enhanced sonography using microbubble contrast agents adds to the sensitivity of the color Doppler ultrasound and may be used to better characterize the nature of the thrombus. Bland versus tumor thrombus may be differentiated on the basis of contrast enhancement during the arterial phase of the study, especially in a thrombus that is noncontiguous with the tumor. Pathological confirmation is usually unnecessary by needle aspiration but may be clinically indicated in some situations, such as when the tumor involving the vessel up-stages the disease and precludes local regional therapy. Contrast-enhanced multi-phase CT (Fig. 3) or MRI (Fig. 4) may be reserved to further characterize PVT extension and to detect the presence of cavernomas, synchronous bowel ischemia, or suspected intra-abdominal malignancy.

Measurement of the hepatic venous pressure gradient through transvenous balloon catheterization may be indicated to assess the portal venous pressure gradient in advanced cirrhotics, in whom intervention might be considered.

It is important to remember that in the initial diagnosis of PVT, 10-15% of patients will present with no known risk factors (Table 1). In these noncirrhotic patients, the presence of myeloproliferative disorder, thrombophilia, or occult malignancy must be considered in the evaluation. Recently, the presence of JAK2 V617 mutation has been demonstrated to be highly suggestive of MPNs and has been found in 5-35% of patients presenting with PVT/SPVT. In these patients, hematologic investigation that includes bone marrow biopsy should be considered to establish MPN diagnosis and guide subsequent treatment. Additionally, exon 9 deletion and/or insertion mutations in the calreticulin gene (CALR) have recently been associated with MPNs. However, the CALR gene mutations are apparently associated with lower risk for PVT/SPVT relative to the JAK2 V617 mutation.
Protein S, protein C, antithrombin antigen, and antiphospholipid antibodies levels are frequently drawn initially to screen for suspected thrombophilia. However, these tests have been shown to be inadequate, and should be replaced by their corresponding functional assays to define thrombophilia phenotypes or by selected genetic testing, such as for factor V Leiden.

**Interventions**

Intervention for PVT depends on defining the patient-specific goals for the intervention, while also weighing the risks and benefits in achieving treatment objectives. Given the delicate balance between thrombosis and bleeding in all PVT patients, interventions may disrupt this equilibrium and affect clinical outcome. The range of treatment for PVT includes close monitoring without intervention, anticoagulation, thrombolysis, thrombectomy, and transjugular intrahepatic portosystemic shunt (TIPS). A clinician’s role is, therefore, to understand the range of options and to recommend the most appropriate treatment based on these considerations.

**Traditional anticoagulants:** Systemic anticoagulation has been the mainstay of VTE treatment. For many decades, standard care was to start with unfractionated heparin or low molecular weight heparin (LMWH), then bridging to oral vitamin K antagonist (VKA) for long-term anticoagulation. Unfractionated heparin has been largely replaced by LMWH in most clinical situations due to the ease of outpatient administration, given subcutaneously once or twice a day, without the need for laboratory monitoring. LMWH has also been used as an alternative for chronic anticoagulation. The recommended dose for enoxaparin is 1 mg/kg every 12 hours (maximum dose 150 mg) and for dalteparin is 10,000 to 18,000 IU once a day (depending on weight). Of note, a previous randomized trial comparing enoxaparin at the standard doses of 1 mg/kg twice a day and 1.5 mg/kg once a day showed that the latter was associated with nearly 4-fold greater risk for nonvariceal bleeding.

Anti-Xa level may be useful in patients with bleeding complications, extreme body weight, renal insufficiency (creatinine clearance <10 mL/min), pregnancy, acute burns, and recurrent thrombosis despite LMWH treatment. However, insufficient evidence currently supports routine monitoring of anti-Xa, even in cancer patients, who are known to have 3-fold higher recurrent thrombosis and 2-fold higher major hemorrhage rate. VKA (warfarin) has been in use in patients with VTE for several decades. In treatment and prevention of VTE and PE, the daily oral VKA dose targets to individualized therapeutic international normalized ratio value of 2.5 (range 2-3).

**Direct-acting oral anticoagulants (DOACs):** DOACs have been in increasing use for treatment of VTE, in a variety of clinical settings. This group of agents includes orally available direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban, betrixaban) and the direct thrombin inhibitor dabigatran. DOACs avert daily subcutaneous injections of LWMHs and the frequent monitoring of VKA. In patients with heparin-induced thrombocytopenia, DOACs represent effective options for anticoagulation. There is no validated clinical monitoring approach for these agents. Dose adjustment for renal impairment should be considered for the direct factor Xa inhibitors at creatinine clearance of 30 mL/min and avoidance at creatinine clearance <15 mL/min. Dabigatran depends on renal clearance and should be avoided at creatinine clearance <30 mL/min.

A comparison of commercially available DOACs is presented in Table 3. In 2015, idarucizumab, a monoclonal antibody fragment that binds dabigatran, was approved by the USA Federal Drug Administration to reverse dabigatran anticoagulation. Most recently, based on the results of the ANNEXA4-A clinical trial, the USA Federal Drug Administration also approvedandexanet-alfa, a recombinant modified human factor Xa fragment that binds factor Xa inhibitors without thrombin cleavage activity, as a reversal agent for direct factor Xa inhibitors. Dabigatran, apixaban, and rivaroxaban have been examined in published PVT clinical trials and case reports (see Supplemental Table 1); edoxaban and betrixaban have not. It should be noted that betrixaban was recently approved in the USA for use in medically frail adults. The discussion of DOACs in management of PVT will be reserved for the section on Management of PVT in Selective Populations (below).

**Pharmacological methods:** Thrombolytic therapy for acute PVT and SPVT has been reported in the literature, as used by the transhepatic, transjugular and retrograde approach through omental veins. These approaches appear to be safe and effective, and have been used primarily in selected nonmalignant, noncirrhotic patients with acute symptomatic thrombosis. The TIPS procedure has been investigated for therapy in the decompression of portal congestion and in the management of portal hypertension due to PVT. The TIPS is placed, with minimal invasiveness, under fluoroscopy into the hepatic vein, through the liver, or into the portal vein via the transjugular approach. TIPS placement has been accepted for the prevention of variceal bleeding and management of refractory ascites. Transplenic access into the portal system for placement of intrahepatic portosystemic shunt has been increasingly used to recanalize the portal vein, and has a high success rate.

**Existing clinical guidelines:** Clinical guidelines for management of PVT have been published by at least two liver
associations\textsuperscript{75,76} several hematology societies\textsuperscript{53,77,78} and others (Table 4).\textsuperscript{37,79} The guidelines vary depending on expert opinions and stringency by which the existing clinical trial data have been evaluated. After comparing the different guidelines, it is essential to note the following:

- All guidelines agree on the recommendation of anticoagulation for acute symptomatic, nonmalignant PVT or SPVT after carefully mitigating risk of gastrointestinal bleeding, especially in patients with mesenteric vein extension associated with evidence of small bowel ischemia.
- Guidelines differ in the length of anticoagulation: for 3-months, 6-months, or indefinitely. In patients with chronic VTE, a strong recommendation could not be made to routinely institute anticoagulation unless an underlying risk factor of neoplasm or thrombophilia could be identified.\textsuperscript{75,76}
- In cirrhotics, anticoagulation should be considered on a case-by-case basis, factoring in risk of bleeding and history of symptomatic intestinal ischemia.
- In liver transplant candidates, the European Association for the Study of Liver\textsuperscript{76} and the Thrombosis Canada and 7th International Coagulation in Liver Disease Conference\textsuperscript{37} recommend the consideration of anticoagulation for 6 months or until transplantation.\textsuperscript{53,76} The American Association for the Study of Liver Diseases offers no recommendation,\textsuperscript{75} although it is accepted in practice to anticoagulate patients prior to liver transplantation.

Given that 70-75% of PVTs occur in the setting of known malignancy (HCC, solid tumors, lymphomas, MPNs), it is worthwhile to revisit the clinical guidelines for the management of cancer and VTE. The National Comprehensive Cancer Network\textsuperscript{80} and American Society of Clinical Oncology have published guidelines for venous thromboembolic diseases in cancer patients.\textsuperscript{81,82} In the 2018 National Comprehensive Cancer Network guideline,\textsuperscript{80} anticoagulation for at least 6 months is recommended in the setting of acute SPVT (defined as symptom and signs \textlesssim 8 weeks and no cavernous transformation/collaterals) without contraindication to anticoagulation. Pharmacomechanical thrombectomy can also be considered in this setting. The American Society of Clinical Oncology’s recommendation only addresses incidentally found VTE, where treatment should be considered on a case-by-case basis.\textsuperscript{81} For cancer patients with newly diagnosed VTE and relatively preserved renal function (creatinine clearance <30 mL/min), treatment with LMWH is preferred over “UHF” for the initial 5 to 10 days. Anticoagulation should be continued for at least 6 months with LMWH, being preferred over VKAs. Long-term anticoagulation with either LMWH or VKA beyond the initial 6 months may be considered for patients with active cancer, such as those with metastatic disease or those receiving chemotherapy.\textsuperscript{81}

### Management of PVT in selected clinical populations

The following sections offer a discussion of selective management considerations, paired with specific discussion on the use of DOACs. A summary table of the trials discussed may be found in Supplemental Table 1.

### Cirrhotic patients without underlying malignancies

#### Prognosis: Acute PVT occurring in cirrhotic patients without evidence of underlying malignancies constitutes 20-25% of all PVT cases. PVTs in this setting can result in both immediate and delayed complications. The impact of PVT on survival of nontransplant patients with liver cirrhosis is conflicting.\textsuperscript{83} In a series of 185 patients with advanced cirrhosis and bleeding esophageal varices, Amitrano et al.\textsuperscript{84} found that the presence of PVT was associated with nonstatistically significant

### Table 3. Comparison of available DOACs\textsuperscript{65,104,105}

| DOAC               | Frequency | Dosing 1 | Dosing 2 | Metabolism | Antidote | Interaction | Adverse Effects | Contraindications |
|--------------------|-----------|----------|----------|------------|----------|-------------|----------------|------------------|
| Dabigatran         | Twice a day | 150 mg BID | 220 mg QDay | Heavy renal clearance | Idarucizumab | P-gp inducers/inhibitors | Dyspepsia; bleeding | Elderly |
| Xarelto\textsuperscript{®} | Daily | 15 mg BID | 21 days then 20 mg QDay | Contraindicated at CrCl < 30 | Andexanet-alfa | *CYP3A4 >> P-gp inducers/inhibitors | Bleeding | Breast feeding; hepatic impaired |
| Eliquis\textsuperscript{®} | Twice a day | 10 mg BID | 7 days then 5 mg QDay | Avoid at CrCl < 15 mL/min | Andexanet-alfa | *CYP3A4 >> P-gp inducers/inhibitors | Bleeding | Breast feeding; hepatic impaired |
| Savaysa\textsuperscript{®} | Daily | 60 mg (or 30 mg) QDay | | Avoid at CrCl < 15 mL/min | Andexanet-alfa | Anticoagulants; P-gp inducers | Rash, abnormal liver function, anemia, bleeding | Breast feeding; hepatic impaired |
| BevyxXa\textsuperscript{®} | Daily | 160 mg initially then 80 mg QDay | | Avoid at CrCl < 15 mL/min. 50% dose for CrCl < 15 mL/min. 50% dose for CrCl between 15 and 30 mL/min | Andexanet-alfa | P-gp inducers | Diarrhea, abnormal liver function | Pregnancy; hepatic impairment; hypersensitivity |

**Abbreviations:** P-gp, P-glycoprotein P; CYP3A4, cytochrome P450.
### Table 4. Summary of existing guidelines for management of PVT

|                         | American Association for the Study of Liver Diseases⁷⁵ | European Association for the Study of Liver⁷⁶ | Thrombosis Canada⁵³ | "ACCP"⁷⁷; British Society of Hematology⁷⁸ |
|-------------------------|--------------------------------------------------------|---------------------------------------------|---------------------|------------------------------------------|
| **Acute PVT/SPVT noncirrhotic** | • Anticoagulate all patients with acute PVT for three-months (IB)  
• Continue long-term therapy in patient with uncorrectable permanent thrombotic risk factors (IB)  
• Consider long-term anticoagulation for patients with thrombus extension into mesenteric veins (IIa-C)  
• Initiate antibiotic promptly in patients with any evidence of infection (IC) | • Initiate immediate anticoagulation with LMWH in the absence of major contraindication (A1)  
• Monitor anti-Xa activity in overweight patients, pregnant or with poor kidney function (A1)  
• Oral VKA are used for long-term anticoagulation targeting INR 2-3 (B1)  
• Anticoagulation therapy should be given for at least 6 month. (A1) | • Anticoagulation is recommended for patients with symptomatic or extensive PVT and in those with extension of the PVT into the superior mesenteric vein  
• The role of anticoagulation in patients with asymptomatic PVT is controversial  
• The duration of anticoagulation in patients with PVT is uncertain | • In patients with symptomatic "SVT", anticoagulation is recommended over no anticoagulation (1B)  
• In patients with incidentally detected SPVT, no anticoagulation is recommended over anticoagulation (2C)  
• British Society of Hematology  
• In acute PVT without cirrhosis anticoagulation is recommended (1C)  
• Patients with acute mesenteric vein thrombosis without peritonitis can be managed conservatively with anticoagulation (1B)  
• There is no evidence as to whether it should be given for 3–6 months or long-term for above |
| **Chronic PVT noncirrhotic** | • Consider long-term anticoagulation therapy in patients with uncorrectable permanent risk factors (IIa-C) | • Consider permanent anticoagulation in patients with a strong prothrombotic condition, or past history suggesting intestinal ischemia, or recurrent thrombosis on follow-up (B2)  
• Long-term anticoagulation in case of underlying MPN | • The role of anticoagulation in patients with portal vein thrombosis and cavernous transformation is very unclear | |
| **PVT in cirrhotics** | • No generalized recommendation  
• Anticoagulation to be considered on case-by-case basis | • Consider anticoagulation at therapeutic dose for at least 6 months (B1)  
• In patients with superior mesenteric vein thrombosis, with a past history suggestive of intestinal ischemia, consider lifelong anticoagulation (C2) | British Society of Hematology  
• In PVT with cirrhosis the risk of anticoagulation will usually outweigh the benefit but an individual decision is needed for each patient. (2C) | |

*(continued)*
An older multicenter, prospective cohort study consisting of 465 bleeding cirrhotic patients, D’Amico and colleagues86 found PVT to be a significant predictor of 5-day failure rate but not 6-week mortality rate. Both these series contained patients with underlying HCC and neither series specifically identified acute PVT or related symptoms. These two studies show that in patients with severe cirrhosis, the finding of PVT, especially if asymptomatic, is associated with high mortality risk. The risk of death may be as high as 15%, related either to uncontrollable bleeding or to irreversible deterioration of underlying liver disease.

Outcomes of treated versus untreated PVT in cirrhotic patients: Senzolo et al.86 reported the only prospective matched cohort study, in which 35 consecutive cirrhotic patients with PVT were treated with anticoagulation and TIPS, and 21 untreated cirrhotic patients with PVT were followed for a mean of 22.5 months. The LMWH nadroparin was started at therapeutic doses for patients found to have acute PVT and continued after complete recanalization at prophylactic doses or for 1 year if recanalization could not be achieved. TIPS was placed in 7 patients, 5 for thrombosis extension. The study included patients with Child-Pugh classes A, B and C patients and having an average model for end-stage liver disease score of 12.6 for the intervention group and 13.7 for patients and having an average model for end-stage liver disease. The findings are:

- No generalized recommendation
- Consider anticoagulation until transplant in liver transplant candidates (B2)
- In liver transplant candidates, who have progressive PVT not responding to anticoagulation, consider referring the patients for TIPS (B2)

- Five variceal bleeding episodes, unrelated to endoscopic variceal ligation, occurred in the nontreatment group, while only one occurred in the treatment group (p = 0.09).
- Intestinal ischemia was described in two cases of the control arm and zero in the interventional arm.
- One major bleeding event occurring in the central nervous system was reported in the anticoagulation arm.

Scheiner and colleagues87 recently reported a retrospective study of 51 patients with nonmalignant cirrhosis. Twelve of these patients were given early short-term anticoagulation (LMWH, VKA or DOACs) and thirty-nine were observed initially and then given long-term anticoagulation. The long-term anticoagulation was given for at least 9 months. The length of early anticoagulation administration was not specified and the decision to start early anticoagulation was started at the discretion of the providers. The 51-patient cohort comprised all CP stages and had a mean MELD of 13.6. The findings are:

- Five variceal bleeding episodes, unrelated to endoscopic variceal ligation, occurred in the nontreatment group, while only one occurred in the treatment group (p = 0.09).
- Intestinal ischemia was described in two cases of the control arm and zero in the interventional arm.
- One major bleeding event occurring in the central nervous system was reported in the anticoagulation arm.

Two other retrospective cohort studies88,89 (Table 3) studied LMWH or VKA in cirrhotic patients with PVT. These two studies showed efficacy of anticoagulation on the recanalization of patients; however, they could not demonstrate statistically significant clinical outcome differences. Bleeding complication rates were low in both studies.

Role of DOACS: The experience of using DOACs in cirrhotic patients with PVT is limited to three retrospective case series90–92 (also see Supplemental Table 1 for summary) and several case reports.93–95 These have been recently reviewed by Priyanka et al.96 The patients are generally asymptomatic.
with Child-Pugh class B and model for end-stage liver disease score of 10. Bleeding events for DOACs within the observational period (16-22 months) were low, being <5% for major bleeding and 10-12% for minor bleeding. Hum et al. 3 compared DOAC anticoagulated patients with VKA-treated patients and concluded that bleeding was less frequent with DOACs. Recanalization of the portal vein was reported in several cases and DOACs did not produce hepatotoxicity. These studies demonstrate safety of DOACs in cirrhotic patients, leading the consensus statements of the 7th International Coagulation in Liver Disease Conference to include DOACs as a therapeutic option for patients with compensated cirrhosis. 37

Summary: The existing clinical evidence does not support routine anticoagulating cirrhotic patients with PVT but without underlying cancers. Even when anticoagulation results in significantly higher recanalization rates and reduced thrombosis recurrence/progression rates, these objectives have not been associated with improvement of clinical outcomes such as mortality rate, portal hypertensive complications, or stabilization/improvement of liver decompensation. Since acute liver decompensation in these patients has been shown to be associated with extreme mortality risk, emergent anticoagulation should only be reasonably considered in patients with evidence of acute liver decompensation after active bleeding has been managed through endoscopic or pharmacomechanical intervention. Anticoagulation appears to be associated with low risk for bleeding, even in very high-risk patients. However, until more definitive evidence emerges, cirrhotics without evidence of liver decompensation should not be routinely treated. In emergent cases, LMWH should be the initial choice due to the availability of effective reversal agent protamine sulfate and should be continued until liver decompensation stabilizes before switching to long-term anticoagulation or discontinued if rapid decompensation persists. If a clinician chooses to place a cirrhotic without clinical deterioration on long-term anticoagulation, DOACs can be considered as a safe, if not preferable, alternative given their safety over LMWH.

Patients with PVT and underlying malignancy (with or without cirrhosis)

Prognosis: In 60-70% of cases, PVT occurs in patients with known malignancy, such as hepatobiliary advanced solid tumors or lymphomas. In a small subset, occult malignancy or MPNs may be found on investigation. In HCC patients, PVT has been reported in 23% of an untreated HCC population and in 35-40% in an autopsy series. PVT occurs more often in patients with metastatic disease, limits cancer therapeutic options, and is associated with significantly shorter overall survival. Similarily, SPVT has been shown by Sogaard and colleagues to be an adverse prognostic indicator for cancer survival.

Outcomes of treated versus untreated PVT in patients with underlying malignancy: The primary objectives of anticoagulation treatment for cancer patients with VTE are to prevent recurrence, extension, or embolism without incurring unacceptable risk for bleeding. LMWH has been established as the preferred treatment option historically, based on the Comparison of Low-molecular-weight heparin versus Oral anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (known as CLOT) trial, which compared LMWH to VKA in patients with active cancer and acute symptomatic proximal deep venous thrombosis or pulmonary embolism. The CLOT trial randomized 672 patients to receive dalteparin or a VKA as treatment and secondary prevention, and demonstrated significantly less recurrent VTE risk (9% vs. 17%) in favor of LMWH with comparable bleeding risk. In a post-hoc analysis, the CLOT investigators also found dalteparin to be associated with survival benefit over VKA in patients with nonmetastatic cancer (the probability of death at 12 months was 20% vs. 36%, p = 0.03); this survival benefit was not found in patients with metastatic cancer.

Role of DOACs: Recently, two DOACs, edoxaban and rivaroxaban, were separately compared to LMWH. These two trials each demonstrated noninferiority of DOAC in comparison with LMWH for recurrent VTE and bleeding risk in cancer patients. It is worthwhile to note that in a series reported by Janczak et al., in which 36 patients with VTE of atypical location were treated with DOACs, recurrence rates and bleeding rates were not different between these patients and other patients who received either LMWH. Of the 36 patients, 26 had SPVT and 54% of these patients had underlying malignancy. All recurrence occurred in patients with underlying cancers.

Summary: In patients with PVT and underlying malignancy, it is reasonable to adhere to existing clinical guidelines for cancer-related VTE with the goals of treating symptoms and preventing recurrence. Even though PVT is often found incidentally, cancer-related hypercoagulability leads to thrombotic progression and related complications, possibly limiting treatment options. LMWH should be considered as the preferred anticoagulant over VKA, although DOACs are reasonable alternatives given the comparable safety. Anticoagulation should be administered for 6 months and could be discontinued if remission is attained following treatment.

Conclusions

Extrapolation of existing clinical trial evidence in PVT research to guide evidence-based practice is difficult, primarily due to heterogeneity of trial population, design, and lack of more meaningful end-points such as mortality, liver decompensation, and bleeding. It underscores the need for more organized nomenclature, classification, and internationally agreed upon trial designs. In this era of genomic medicine, novel predictive and prognostic markers should also be sought to define clinical indications for treatment. Currently, LMWH remains the standard treatment for noncancer patients with severe liver cirrhosis and evidence of acute liver decompensation. In all other situations, the use of DOACs appears to be safe and likely noninferior to LMWH.

Conflict of interest

The author has no conflict of interests related to this publication.

Author contributions

Drafting of the manuscript (MW), revision of the manuscript for important intellectual content (MW and MT), and contribution of images for figures (MS).

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