# PORTAL VEIN THROMBOSIS

CHI Formulary Development Project

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**February 2024**

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## Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates

- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

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# Abbreviations

| | |
|---|---|
| AAPT | Activated Partial Thromboplastin Time |
| CHI | Council of Health Insurance |
| CT | Computed Tomography |
| DOAC | Direct oral anticoagulant |
| DVT | Deep Vein Thrombosis |
| EMA | European Medicines Agency |
| FDA | Food and Drug Administration |
| HIT | Heparin-Induced Thrombocytopenia |
| IDF | Insurance Drug Formulary |
| INR | International Normalized Ratio |
| LMWH | Low Molecular Weight Heparin |
| MRI | Magnetic Resonance Imaging |
| PCC | Prothrombin Complex Concentrates |
| PE | Pulmonary Embolism |
| PVR | Portal Vein Recanalization |
| PVT | Portal Vein Thrombosis |
| SFDA | Saudi Food and Drug Authority |
| TIPS | Transjugular Intrahepatic Portosystemic Shunt |
| TPO-R | Thrombopoietin Receptor |
| UFH | Unfractionated Heparin |
| ULN | Upper Limit of Normal |
| VKA | Vitamin K antagonist |
| VTE | Venous Thromboembolism |

## Executive Summary

Anatomically, the spleen is drained by the splenic vein, while the small intestine is drained pas the superior mesenteric veins. Those veins eventually meet and form the portal vein. In cases of cirrhosis and/or prothrombotic disorders (**Table 1**), a thrombus can occur and occlude the portal vein. This situation is called portal vein thrombosis (PVT). It may occur acutely or chronically.

**Table 1**. Causes of Portal Vein Thrombosis (PVT)

| |
|---|
| Abdominal sepsis |
| Abdominal surgery |
| Behcet's syndrome |
| Cirrhosis |
| Collagen vascular diseases (e.g., lupus) |
| Compression or invasion of the portal vein by tumor (e.g., pancreatic cancer) |
| Endoscopic sclerotherapy |
| Hepatocellular carcinoma |
| Inflammatory bowel disease |
| Inherited thrombophilias |
| Myeloproliferative syndromes |
| Omphalitis |
| Oral contraceptives |
| Pancreatic islet cell transplantation |
| Pancreatitis |
| Paroxysmal nocturnal hemoglobinuria |
| Pregnancy |
| Retroperitoneal fibrosis |
| Transjugular intrahepatic portosystemic shunt |
| Trauma |

## I. Acute portal vein thrombosis in adults: clinical manifestations, diagnosis, and management

Acute PVT is characterized by the sudden onset of portal vein occlusion by a thrombus. Occlusion can be complete or partial. The thrombus may only involve the portal vein or extend to mesenteric and splenic veins. Features of chronic PVT, such as collateral circulation (cavernous portal transformation) or portal hypertension, are absent. A PVT of unknown unset but without features of chronic PVT is referred to as being "recent"[1]. Management of acute and recent PVT is similar.

### a. Clinical manifestations

The extent of the obstruction and the speed of its development determine the clinical manifestations of acute PVT.

Symptoms

- Silent clinical picture: diagnosis of PVT occurs during a radiologic examination for other reasons (e.g., acute pancreatitis).
- Abdominal pain of sudden onset or progressive over a few days.
- Fever and dyspeptic symptoms.
- Variceal bleeding in case of cirrhosis.
- Spiking fevers, chills, and a painful liver suggest septic PVT (acute pyelophlebitis).
- Symptoms related to conditions predisposing to PVT development (e.g. pancreatitis).
- Colicky abdominal pain and diarrhea in case of superior mesenteric vein occlusion.
- Ischemia and infarction in case of proximal mesenteric venous arches occlusion, with abdominal pain radiating to the back, lasting beyond 7 days, associated with abdominal distention and ascites, and bloody diarrhea.
- For patients with underlying inflammatory bowel disease, acute PVT presentation may mimic a disease flare.

Physical examination

Physical examination is normal in most cases of acute PVT. However, ileus and abdominal distension without other signs of intestinal obstruction may occur. Guarding is typically absent unless the PVT is caused by an intra-abdominal inflammatory process or if intestinal infarction has occurred. Infarction is also characterized by signs of ascites on examination (e.g. fluid wave). In patients with cirrhosis, stigmata of chronic liver disease (e.g. palmar erythema or signs of hepatic encephalopathy) may be present.

Laboratory testing

- Increase in plasma levels of acute phase reactants
- Liver tests are typically normal (transient and moderate increase in aminotransferases un some cases): hepatic arterial blood flow is usually able to compensate for decreased portal inflow.
- In cases of bowel ischemia: metabolic acidosis, signs of renal or respiratory failure, leukocytosis, and an increased hematocrit due to hemoconcentration[2].
- In cases of septic PVT: blood cultures are often positive for Bacteroides fragilis or Escherichia coli.
- In cases of cirrhosis: increased bilirubin, low platelet count, prolonged international normalized ratio (INR), or renal insufficiency.

Abdominal imaging

Abdominal imaging may show evidence of portal venous occlusion and intestinal ischemia, and possibly an underlying focus of infection or multiple, small liver abscesses in patients with septic PVT.

**b. Diagnosis**

Acute PVT diagnosis is based on abdominal imaging that demonstrates portal venous occlusion without the radiographic findings of chronic PVT (cavernous portal transformation). Typically, a contrast-enhanced abdominal computed tomography (CT) is ordered when acute PVT is suspected, in order to confirm the diagnosis, evaluate for predisposing conditions, measure the extent of the thrombosis, determine the anatomy of collaterals and detect evidence of intestinal infarction. A Doppler ultrasound is a reasonable initial approach in cases of low suspicion for PVT. If it suggests acute PVT, then an abdominal CT can be ordered. For patient who cannot undergo a CT, an abdominal magnetic resonance imaging (MRI) is an alternative. If both CT and MRI are contraindicated or not available, Doppler ultrasound is used but may not detect predisposing conditions or ischemia. Finally, portal venography or superior mesenteric angiography can be used to diagnose acute PVT, but angiography is invasive and is generally not required[3].

- Abdominal CT: without contrast, the CT scan shows hyperattenuating material in the portal vein. A contrast-enhanced CT is often needed to establish diagnosis, due to the difficulty to distinguish the density of the thrombus from the vessel wall: it reveals lack of luminal enhancement, increased hepatic enhancement in the arterial phase, and decreased hepatic enhancement in the portal phase.
- MRI angiography: shows a filling defect that partially or completely occludes the vessel lumen in the portal venous phase.

- Abdominal ultrasound with Doppler: shows hyperechoic material within the portal vein, with distension of the portal vein and its tributaries (portal vein diameter: > 13 to 55 mm in diameter). The portal vein does not vary in diameter during respiration. Ultrasound misses the thrombus in 1/3 of PVT patients. Consequently, Doppler imaging should also be used: it shows the absence of flow in some or all of the vessel lumen.

Identification of predisposing conditions

Prothrombotic states should be suspected and evaluated in patients with PVT who do not have cirrhosis or who have compensated cirrhosis (Child class A or B). However, in case of decompensated cirrhosis, PVT is frequent and search for other predisposing conditions is not necessary.

**c. Differential diagnosis**

- Invasion of the portal vein by an abdominal malignancy (hepatocellular carcinoma): most frequently
- Constriction of the portal vein within a tumor (pancreatic cancer or cholangiocarcinoma)

In these cases, the thrombus within the portal vein is a secondary event and is termed malignant PVT. Imaging is helpful in order distinguish benign PVT from malignant PVT. The distinction is important in patients with cirrhosis and hepatocellular carcinoma who are being considered for liver transplantation (LT), malignant PVT being a contraindication to LT. The findings that suggest malignant PVT include an increased alpha fetoprotein, a portal vein diameter > 23mm, the enhancement of endoluminal material during the arterial phase of contrast injection, an arterial-like pulsatile flow on Doppler ultrasound, and disruption of the vessel walls or tumor encroaching on the portal vein[4,5].

**d. Management**

The primary therapy of acute PVT is **anticoagulation** and, when possible, treatment of predisposing conditions. Anticoagulation aims to prevent extension of the clot and to allow for recanalization, so that intestinal infarction and portal hypertension do not develop. Anticoagulation for acute PVT may be beneficial for patients with cirrhosis, as opposed to chronic PVT. However, screening for esophageal varices prior to initiating anticoagulation is warranted in patients with cirrhosis.

Low molecular weight heparin (LMWH) is the first-line therapy to achieve rapid anticoagulation. Once the patient is stable and no invasive procedures are planned, they may be switched to an oral anticoagulant. If warfarin is used, INR should be between 2 and 3. In case of cirrhosis, non-warfarin-based therapy is preferable because the INR may not reflect the patient's level of anticoagulation.

If there is a transient or correctable thrombotic risk factors (such as pancreatitis) or if no thrombotic risk factor is identified, it is suggested to use of anticoagulation for 6 months rather than long-term anticoagulation. In case of permanent thrombotic risk factors that cannot be corrected, long-term anticoagulation is preferred. Long-term therapy may also be suggested in patients with acute PVT extending into the mesenteric veins, given the risk of intestinal infarction.

Antibiotic therapy is necessary, in addition to anticoagulation, in patients with septic PVT. Finally, surgical exploration is required in case of infarction in the setting of acute PVT.

Complications of anticoagulation

Bleeding is the main complication of anticoagulation. Studies in patients with acute PVT who do not have cirrhosis have reported bleeding rates of 0 to 6% (minor bleeding mostly)[6]. The risk of bleeding increases in case of cirrhosis.

Alternatives to anticoagulation

- Streptokinase or tissue plasminogen activator: administered locally by a catheter through a transjugular transhepatic or percutaneous transhepatic route[7].
- Thrombolysis (with or without thrombectomy): benefit is uncertain, since the natural history of acute PVT is not well defined. Moreover, serious complications have been reported (significant bleeding and death)[8].
- Surgical thrombectomy: reserved for patients who are undergoing surgery for intestinal infarction.

**e. Prognosis**

Prognosis is usually good if treatment of acute PVT is initiated early, prior to the onset of intestinal infarction. Symptoms and systemic inflammatory response syndrome will start to resolve within hours to days after starting anticoagulation. Intestinal infarction is usually prevented if the superior mesenteric vein remains patent or recanalizes. Similarly, if the portal trunk and at least one of its branches remains patent or is recanalized, portal hypertension will not occur.

In the absence of treatment, intestinal infarction may develop, though the frequency remains undefined. Consequently, intestinal perforation, peritonitis, shock, multiorgan failure, and death may occur if treatment is not provided rapidly.

Finally, acute PVT may become chronic in patients without intestinal ischemia who remain untreated (such as patients with asymptomatic acute PVT). Frequency of spontaneous recanalization in the absence of treatment remains unknown.

## II. Chronic portal vein thrombosis in adults: Clinical manifestations, diagnosis, and management

When acute PVT does not resolve (with or without treatment), chronic PVT appears. Chronic PVT leads to the development of collateral blood vessels, responsible for blood flow in a hepatopetal manner around the area of obstruction. This is known as cavernous transformation of the portal vein or portal cavernoma. On CT imaging, cavernous transformation appears as multiple caveolar orifices. Complications of chronic PVT include portal hypertension and portal cholangiopathy.

### a. Clinical manifestations

Symptoms

- Asymptomatic: chronic PVT is discovered incidentally upon abdominal imaging for other reasons.
- Gastrointestinal bleeding (hematemesis, melena, or hematochezia): most common symptom. It is related to esophageal or gastric varices, which are frequent in chronic PVT. Varices may be otherwise asymptomatic.
- Symptoms of portal hypertension or portal cholangiopathy (complications of chronic PVT). Portal cholangiopathy (or portal biliopathy) occurs in case of longstanding chronic PVT. It is due to compression of the large bile ducts by the venous collaterals that are present in chronic PVT). Patients are usually asymptomatic, but may develop biliary complications such as pruritus, obstructive jaundice, and cholecystitis. The constellation of jaundice, abdominal pain, and fever suggests cholangitis.
- Intestinal ischemia and infarction (in case of extension of the clot into the superior mesenteric vein): abdominal pain radiating to the back, abdominal distension from ascites, bloody diarrhea.
- Manifestations related to underlying conditions that predispose to PVT, such as cirrhosis.

Physical examination

It may be normal in chronic PVT. However, signs of portal hypertension are frequent (e.g. splenomegaly, which may be massive), as are signs of underlying cirrhosis (e.g. palmar erythema or a fluid wave from ascites). Subclinical encephalopathy is found in approximately 50% of patients with PVT without cirrhosis, but overt encephalopathy is uncommon and is typically seen following gastrointestinal bleeding, in case of renal failure, or in case of sepsis in older adults[9,10].

Laboratory testing

- Liver biochemical tests (e.g. serum aminotransferases): usually normal or only slightly increased.
- Hepatic synthetic function tests: preserved in the absence of cirrhosis, with the exception of hypoalbuminemia. Hypoalbuminemia may be found after fluid resuscitation for gastrointestinal bleeding. Liver failure occurs in patients who have concomitant cirrhosis.
- Anemia, thrombocytopenia, and leukopenia (signs of hypersplenism)
- Elevated alkaline phosphatase and bilirubin (cholestatic pattern) in case of portal cholangiopathy.

Abdominal imaging

Imaging in chronic PVT reveal cavernous transformation of the portal vein and filling defects.

**b. Diagnosis**

Diagnosis of chronic PVT is based on abdominal imaging. Initial imaging is abdominal ultrasound with Doppler imaging, followed by a contrast-enhanced CT scan or MRI to confirm the diagnosis and to look for predisposing conditions (e.g. hepatocellular carcinoma). Doppler ultrasound is used first because of its low cost and ability to identify biliary pathology related to abdominal pain. However, if chronic PVT suspicion is high or if abdominal pain is diffuse, a contrast-enhanced CT or an MRI may be performed first. Serologic evaluation for predisposing conditions should also be performed (hypercoagulability workup).

- Abdominal ultrasound with Doppler imaging: shows hyperechoic material within the portal vein that may extend into the mesenteric or splenic veins, dilation of the portal vein and its tributaries, absence of flow within the portal vein, a mass of tortuous vessels at the porta hepatis or within the liver[11]. The velocity of blood flow within those vessels is usually less than that in a normal portal vein.
- Abdominal CT: shows a network of intertwined, densely packed veins in the hepatoduodenal ligament and porta hepatis. The thrombosed portal segment may not be visualized, but small veins may be enhanced [25]. Communication between collateral vessels and intrahepatic portal veins may be seen[12].
- Abdominal MRI: shows portal vein occlusion, collateral veins around the porta hepatis.
- MRI angiography: shows PVT as a filing defect, partially or completely occluding the vessel lumen in the portal venous phase[13].

- Angiography: considered if the diagnosis of chronic PVT remains doubtful after standard imaging, or if shunt surgery is planned. Contrast injection reveals PVT as a filling defect or non-opacification of the portal vein or one of its branches. With cavernous transformation, venous branches are often filled by the collateral veins. Use of angiography became rare with the increasing use of CT scan and MRI.

Identification of predisposing conditions

The existence of a predisposing condition (hypercoagulable state) should be suspected, and a hypercoagulability workup done in all patients with PVT who do not have cirrhosis or who have compensated (Child-Pugh class A or B) cirrhosis. In case of decompensated cirrhosis, the prevalence of PVT being high, the decision to do a workup for a genetic basis for hypercoagulability should be individualized. It is usually reserved for recurrent thrombotic events, if thrombosis occurs in more than one vascular bed, or if there is a family history of thrombotic disorders.

**c. Differential diagnosis**

- Invasion of the portal vein by an abdominal malignancy (hepatocellular carcinoma): most frequently;
- Constriction of the portal vein within a tumor (pancreatic cancer or cholangiocarcinoma);
- Cholangiocarcinoma or pancreatic cancer: resemblance with portal cavernomas on imaging. Endoscopic ultrasound and magnetic resonance angiography are helpful to distinguish these conditions.

In these cases, the thrombus within the portal vein is a secondary event and is termed malignant PVT. Imaging is helpful in order distinguish benign PVT from malignant PVT. The distinction is important in patients with cirrhosis and hepatocellular carcinoma who are being considered for LT, malignant PVT being a contraindication to LT. The findings that suggest malignant PVT include an increased alpha fetoprotein, a portal vein diameter > 23mm, the enhancement of endoluminal material during the arterial phase of contrast injection, an arterial-like pulsatile flow on Doppler ultrasound, and disruption of the vessel walls or tumor encroaching on the portal vein[14].

**d. Management**

The management of chronic portal vein thrombosis (PVT) depends on the presence of predisposing conditions and the patient's comorbidities. Basic management includes screening for esophageal varices and treating complications of portal hypertension and portal cholangiopathy. In addition, anticoagulation may be indicated for some patients.

Screening for varices

Screening for esophageal varices should be performed in all patients with chronic PVT. Nonselective betablockers or endoscopic therapy are suggested treatment options to decrease the risk of variceal bleeding, even though it has not been specifically studied in patients with varices due to PVT.

Anticoagulation

The aim is to prevent recurrent thrombosis and thrombus extension, maintain splanchnic venous drainage, relieve symptoms, and promote recanalization in patients with cirrhosis. It is important to note that patients with chronic PVT are at risk for recurrent thrombosis and for bleeding as well. The decision to start anticoagulation must be made on a case-by-case basis.

Selecting patients for treatment

The decision to start anticoagulation therapy is based on the following criteria:

- Patient's risk of bleeding (e.g. large varices)
- Patient's risk of a thrombotic event (e.g. underlying prothrombotic disorder)
- Chances to survive a bleed or a thrombotic event
- LT waiting list
- Symptoms (e.g. abdominal pain)

Long-term anticoagulation is offered to patients who are at increased risk for recurrent thrombosis based on their clinical history or laboratory studies. Increased risk for recurrent thrombosis is seen in patients with inherited prothrombotic disorders, decompensated cirrhosis, or malignancy. In patients with a history of gastrointestinal variceal bleeding or large varices who are at increased risk for bleeding (particularly in cirrhosis), anticoagulation is given only if adequate measures to prevent recurrent bleeding can be implemented. Nonselective beta blockers are preferred over variceal ligation for prophylaxis in these patients, because of the potential risk of bleeding from esophageal ulcers that form when the bands used for variceal ligation slough off. Anticoagulation is also offered to patients with PVT and advanced cirrhosis who are awaiting transplantation and do not have contraindications to anticoagulation.

Expectant management is preferred to anticoagulation in patients who are at increased risk for bleeding (large varices without adequate prophylactic measures to prevent bleeding), are unlikely to survive a bleeding episode, or are not at increased risk for recurrent thrombosis. Patients not at increased risk for thrombosis are those with PVT that developed due to a transient event, such as transient hypovolemia, without any underlying disorder that predisposes to thrombosis.

Choice of agent

Enoxaparin is preferred to warfarin: it has a shorter duration of action, less variability in anticoagulation, decreased need for monitoring, and decreased difficulty when managing patients around the time of LT. The alternative is an oral anticoagulant. When warfarin is chosen, the goal INR is 2 to 3[15].

Direct oral anticoagulant (DOAC) therapy is an alternative to both enoxaparin and warfarin. DOAC use is individualized: benefits (oral administration, decreased need for laboratory monitoring) and risk of bleeding are discussed with patients.

Efficacy

- Patients without cirrhosis

Several studies have showed that anticoagulation for PVT in the absence of cirrhosis resulted in favorable outcomes[9,16,17]. In a trial in particular, rivaroxaban resulted in lower risk of recurrent thrombosis compared with no anticoagulation after a median follow up of 11.8 months. Bleeding risk was not significantly different between groups. Although DOACs were not associated with an increased risk of bleeding, the theoretical risk is discussed with patients at treatment initiation.

- Patients with cirrhosis

Anticoagulation may be beneficial for patients with cirrhosis and portal vein thrombosis, as suggested by observational studies. A meta-analysis by Loffredo et al. including 353 patients with cirrhosis and PVT showed that patients treated with anticoagulants (LMWH or warfarin) had higher rates of partial or complete recanalization compared with untreated patients[18]. The overall rate of bleeding was similar in the anticoagulated and untreated patients. Variceal bleeding risk was assessed in four studies including 158 patients: variceal bleeding rate was lower in anticoagulated patients compared with untreated patients. A dedicated clinical trial is essential to validate the efficacy and safety of anticoagulant therapy in this setting and identify the target population.

In the setting of future LT, data on the use of anticoagulation is limited. A study of 19 patients with cirrhosis who were awaiting LT, anticoagulation was associated with restoration of portal vein patency in 10, compared with 0 of 10 historic controls[19]. Postoperative complications were also reduced with anticoagulation use.

Management of complications

Chronic PVT complications include variceal bleeding, ascites, hepatic encephalopathy, pruritus, and cholangitis. Management of these complications is similar to cases without PVT.

Variceal hemorrhage is treated with endoscopic therapy. Definitive salvage therapy is advised for patients who have repeated hemorrhage despite adequate endoscopic

treatment, who have isolated varices in the gastric fundus, or ectopic varices (splenectomy or surgical shunting depending upon the site of bleeding). Surgery corrects the varices and is usually well-tolerated: liver function is typically preserved in the absence of cirrhosis. Recurrent hemorrhage due to portal hypertension related to extensive PVT is not frequent. In this scenario, if a collateral vessel is large enough to place a transjugular intrahepatic portosystemic shunt (TIPS), decompressing the portal system using TIPS should be made. However, data related to the efficacy of TIPS is scarce.

Obstruction level dictates the choice of surgery. Splenectomy is used when there is splenic vein thrombosis and bleeding gastric varices; when there is diffuse thrombosis of the portal, mesenteric, and splenic veins, a non-shunting operation, such as a modified Sugiura procedure (transection of the esophagus and devascularization of the paraesophagogastric region) can be performed. When the superior mesenteric vein is patent, a mesocaval shunt combined with splenectomy and left gastric vein ligature can be performed. Finally, TIPS has been shown to be technically feasible in some cases of extrahepatic PVT (e.g. patients with cavernous transformation in whom the thrombosed vein can be accessed, dilated, and stented). It may also be considered in selected cases with symptoms due to portal hypertension, resistant to other treatments. Adequate decompression of the portal vein remains unpredictable.

When PVT is the cause of bowel ischemia, surgical decision is individualized and aims to decompress the portal vein and preserve the bowel.

**e. Prevention in patients with cirrhosis**

Prevention of PVT in cirrhotic patients is based on optimization of hepatic function, reducing portal venous pressure, and increasing portal flow, which diminishes stasis.

**f. Prognosis**

In the absence of cirrhosis or malignancy, prognosis is good when treatment of PVT is performed. A study by Condat et al. showed that among 136 patients with chronic PVT who did not have cirrhosis or an underlying malignancy, less than 5 % of patients followed for five years died from PVT complications (intestinal infarction or gastrointestinal bleeding)[9].

Anticoagulation in patients with chronic PVT aims to prevent recurrent thrombosis and thrombus extension, maintain splanchnic venous drainage, relieve symptoms, and promote recanalization in patients with cirrhosis. However, these patients who are at risk for recurrent thrombosis are also at risk for bleeding. Consequently, the decision to start anticoagulation must be made on a case-by-case basis.

**Table 2**. Summary of SFDA-Registered Drugs for the Management of Portal Vein Thrombosis

| Drug | Indication | Dose | Health Technology Assessment (HTA) |
|---|---|---|---|
| **Unfractionated heparin (UFH)** | Treatment of Portal Vein Thrombosis | 80 U/kg IV bolus, then continuous infusion of 18 U/kg/h<br>Or 5000 U IV bolus, then continuous infusion of 1300 U/h<br>Or 250 U/kg (or 17500 U) subcutaneously (SC), then 250 U/kg/12h<br><br>Level of APTT should increase to 1.5–2.5 × ULN | There are no recommendations issued by the HTA bodies for UFH. |
| **Enoxaparin (LMWH)** | Treatment of Portal Vein Thrombosis | 1mg/kg/12h SC | There are no recommendations issued by the HTA bodies for enoxaparin. |
| **Warfarin** | Treatment of Portal Vein Thrombosis | Initial dose: 2-5mg/day PO for 2 days or 10mg PO for 2 days<br>Initiate warfarin on day 1 or 2 of LMWH or UFH and overlap until desired INR, then discontinue heparin. | There are no recommendations issued by the HTA bodies for warfarin. |
| **Fondaparinux** | Treatment of Portal Vein Thrombosis | < 50kg: 5mg SC once daily<br>50-100kg: 7.5mg SC once daily<br>>100kg: 10mg SC once daily | There are no recommendations issued by the HTA bodies for fondaparinux. |
| ***Direct Oral Anticoagulants (DOACs)*** | | | |

| | | | |
|---|---|---|---|
| **Dabigatran** | Treatment of Portal Vein Thrombosis | 150 mg twice daily | There are no recommendations issued by the HTA bodies for dabigatran. |
| **Apixaban** | Treatment of Portal Vein Thrombosis | 10 mg twice daily for 7 days followed by 5 mg twice daily | Positive Recommendation from CADTH |
| **Edoxaban** | Treatment of Portal Vein Thrombosis | 30-60 mg once daily | There are no recommendations issued by the HTA bodies for edoxaban. |
| **Rivaroxaban** | Treatment of Portal Vein Thrombosis | 15 mg twice daily with food for 21 days followed by 20 mg once daily with food | There are no recommendations issued by the HTA bodies for rivaroxaban. |

**Table 3.** Non-SFDA-Registered Drugs for the Management of PVT

| Medication | Indication | Line of Therapy | Level of Evidence/Recommendation |
|---|---|---|---|
| **Streptokinase** | Alternatives to anticoagulation in Portal Vein Thrombosis | **2nd** | N/A |

This report compiles all clinical and economic evidence related to PVT according to the relevant sources. The ultimate objective of issuing PVT guidelines by the Council of Health Insurance (CHI) is to update the IDF (CHI Drug Formulary) with the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to patients with PVT in Saudi Arabia.

The main focus of the review was on North American, European, and other international guidelines issued within the last five years. Main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of the current medications in PVT were reviewed and summarized under each drug therapy table in Section 2.0. These include the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC).

It is important to emphasize that these treatment approaches serve as general recommendations. The appropriate treatment plan for each patient should be determined based on the specific type of PVT, as well as their overall health status. To provide a concise overview, the report will feature in section 3 a synthesis of key recommendations, focusing on the relevant drugs that align with these guidelines.

# Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

## 1.1 KSA Guidelines

To date, no guidelines have been published by Saudi bodies for the management of PVT.

## 1.2 North American Guidelines

### 1.2.1 American Association for the Study of Liver Diseases (AASLD) Practice Guideline on Vascular Liver Disorders, Portal Vein Thrombosis, and Procedural Bleeding in Patients with Liver Disease (2020)

This American Association for the Study of Liver Diseases (AASLD) Guidance provides a data-supported approach to the management of vascular liver disorders, portal (PVT) and hepatic vein thrombosis (HVT), and procedural bleeding in patients with liver disease[20]. For the purpose of this report, only recommendations related to the management of PVT have been included.

**Goals of therapy and rationale for treatments - guidance statements**

- All patients with recent PVT and concern for intestinal ischemia: immediate consultation with surgery, critical care, interventional radiology, and hematology is recommended. Anticoagulation is paramount. In case of intestinal infarction, surgery is needed.
- Patients without cirrhosis and with recent PVT: directed antithrombotic therapy should be considered, in order to prevent intestinal ischemia and the development of chronic PVT with portal hypertension.
- Patients with cirrhosis: treatment indications for PVT without ischemic symptoms relies on weak clinical trial data. Therapeutic decisions are made on a case-by-case basis, taking into account expected benefit and minimization of clot extension risk, which could lead to progression of portal hypertension or hinder LT.
- Patients with cirrhosis who have recent thrombosis of small intrahepatic sub-branches of the PV or minimally occlusive (<50% obstruction of the lumen) thrombosis of the main PV: observation without therapy, with serial imaging every 3 months. Treatment for progressive clot should then be considered in this setting.

- Patients with cirrhosis with recent occlusive or partially occlusive (>50% obstruction of the lumen) thrombosis of the main PV or mesenteric veins: antithrombotic therapy should be considered to avoid thrombosis progression that may hinder a future LT or provoke progression of portal hypertension.
- Patients with chronic complete occlusion of the main PV or cavernous transformation of the PV with established collaterals: no established benefit of anticoagulant or interventional therapy. Treatment should be targeted at management of portal hypertension complications.
- Endoscopic variceal ligation: can be performed safely without stopping therapeutic anticoagulation. Available safety data suggest that anticoagulation should be initiated as soon as possible and not delayed until variceal eradication or adequate beta-blockade is achieved.

**PVT treatment options**

Thrombolysis and interventional vascular procedures

- Local or systemic thrombolytic therapy: reserved for very selected cases of recent PVT in whom intestinal ischemia persists despite anticoagulation.
- Portal vein recanalization (PVR) followed by TIPS:
    - Considered in LT candidates with chronic PVT that impedes a physiological anastomosis between the graft and recipient PV. A multidisciplinary management process is needed in this case, with surgical and interventional radiology.
    - Considered in patients with chronic PVT and recurrent bleeding and/or refractory ascites not manageable medically or endoscopically.

Medical therapies for PVT

Historically, the choice of anticoagulation for patients with PVT has been limited to unfractionated heparin (UFH), LMWH, and vitamin K antagonists (VKA), such as warfarin. Nowadays, DOACs are a new therapeutic option, which complexifies treatment decisions, especially that data remains scarce in this population. Recommendations rely on smaller cohort studies and extrapolation from anticoagulation experience in other populations.

a. Patients with Cirrhosis

*Traditional anticoagulants*

Most studies have examined the effect of LMWH and/or VKAs in patients with compensated cirrhosis without standardized endpoint definitions and varying

treatment strategies. In particular, bleeding outcomes are not standardized, and comparative data assessments are subject to significant bias.

Nery et al. described spontaneous recanalization in up to 40% of patients with cirrhosis who develop PVT, typically within 3 months[21].

A meta-analysis by Loffredo et al.[18] showed that complete PVR occurred in 42% of patients with anticoagulation therapy alone and 13% of patients who did not receive anticoagulation or vascular intervention. It also demonstrated a relationship between recanalization and time to initiation of therapy, with < 6 months being optimal.

Patients with cirrhosis who are candidates for LT may be treated with anticoagulation in order to recanalize the portal vascular system before LT. Due to familiarity with these molecules and existence of reversal strategies, LMWH and VKAs are usually used in this setting. Limitations for LMWH and VKAs should be kept in mind (Table 9). However, factor replacement with FFP or prothrombin complex concentrates is needed for emergency reversal at the time of transplant, which may lead to volume overload or overcorrection to a hypercoagulable state, respectively.

The benefit of anticoagulation for PVT is less clear outside the situation of LT, but traditional anticoagulation likely promotes recanalization, which may benefit select patients, especially those with associated portal hypertension symptoms. The duration of therapy remains unclear, and dosing is not standardized. Importantly, the risk of anticoagulation is undefined, but overall bleeding rates (unrelated to portal hypertension) appear comparable to those of patients without cirrhosis, and anticoagulation does not seem to increase severity of bleeding or overall risk of mortality in patients who do develop gastrointestinal bleeding.

*Direct oral anticoagulants (DOACs)*

Little is known about the pharmacodynamics of DOACs in cirrhosis, due to the exclusion of patients with cirrhosis from clinical trials comparing DOACs versus VKAs and LMWH for prophylaxis and treatment of VTE or atrial fibrillation. A few in vitro and in vivo studies have shown differences in anticoagulant potency when measured by thrombin generation assay. Larger in vivo studies are needed. In clinical practice, DOACs have been used in select patients with well-compensated cirrhosis. Overall, DOACs seem to have a similar safety profile in patients with compensated cirrhosis compared to patients without cirrhosis. Consequently, their use is expanding in patients with all indications for anticoagulation, including PVT[22,23].

The availability of direct reversal agents may decrease some fears concerning bleeding (e.g. successful use of idarucizumab for reversal of dabigatran in a patient undergoing LT)[24].

Moreover, two studies have directly compared DOACs to VKAs in different cohorts of patients with cirrhosis and PVT. Despite the low level of evidence, bleeding rates were not significantly higher in patients treated with DOACs[25,26] .

b. Patients without cirrhosis

*Traditional anticoagulants*

Data on anticoagulation for PVT in non-cirrhotic patients is limited. In 2010, a large prospective trial by Plessier and collaborators examined efficacy and safety of anticoagulation (LMWH, VKAs) in 95 consecutive patients with recent PVT without cirrhosis. Complete recanalization was obtained in 38% of the cohort, progression of thrombus with intestinal infarction occurred in 2 patients, and 9 patients developed bleeding on anticoagulation[27].

Large international registry database analyses indicate that non-cirrhotic patients with PVT are at higher risk of morbidity and mortality from thrombotic events and that the overall risk of bleeding from anticoagulation is low[28,29].

*Direct oral anticoagulants (DOACs)*

The use of DOACs as therapy for PVT in non-cirrhotic patients is now becoming commonplace. Several retrospective, small studies have demonstrated the successful use of DOACs in this setting. A large, retrospective, single-center cohort study demonstrated that DOAC therapy had superior efficacy (rates of thrombus resolution) and less major bleeding when compared to warfarin (Naymagon 2020). DOAC use has many advantages over warfarin, such as the lack of a need for monitoring and predictable anticoagulant effect[30].

<u>Guidance statements</u>

- The choice of agent for anticoagulant therapy (LMWH, VKAs, and DOACs) in PVT should be individualized. Consultation with a hematologist and/or expert hepatologist should be considered in deciding on anticoagulant agents and duration.
- Therapeutic anticoagulation in patients with cirrhosis seems to have similar non-portal hypertensive bleeding complication rates compared to the general population. Moreover, bleeding related to portal hypertension in patients with cirrhosis appears unchanged by the use of anticoagulants.
- DOACs are emerging as a common therapy in general for thrombosis. PVT data remain sparse regarding safety and efficacy of these agents in patients with and without cirrhosis. In cirrhotic patients, caution is advised in patients with advanced portal hypertension, and expert consultation is recommended.

### 1.2.2 American College of Gastroenterology (ACG) Clinical Guideline: Disorders of the Hepatic and Mesenteric Circulation (2020)

Key concept statements based on expert opinion and review of literature and specific recommendations based on PICO/GRADE analysis have been developed by the ACG to aid in the management of vascular liver disorders. These recommendations and guidelines should be tailored to individual patients and circumstances in routine clinical practice[31].

**Etiology and prevalence**

Thrombosis of the portal and/or mesenteric veins is related to Virchow's triad.

The most common cause of PVT in non-cirrhotic patients is thrombophilia[27]. The most common inherited causes of thrombophilia in the United States are factor V Leiden mutation and Prothrombin G20210A gene mutation. Other inherited causes of reduced anticoagulant activity, including deficiency of antithrombin, PC, or protein S, and antiphospholipid syndrome, are equally prevalent. 25% of patients with PVT have myeloproliferative neoplasms. Testing for 1849G to 1849T point mutation of the tyrosine kinase janus kinase 2 (JAK2) gene in myeloid cells is very specific and accurate in making a diagnosis of myeloproliferative neoplasms[32,33]. Use of oral contraceptives is a risk factor for development of PVT (Table 4). Other less common risk factors such as Behçet disease and celiac sprue may also cause PVT. Some patients may have more than one cause of PVT.

**Table 4**. Causes of Portal or Mesenteric Vein Thrombosis

| **Thrombophilia** |
|---|
| Malignancy of any intraabdominal organ |
| Myeloproliferative neoplasm |
| Paroxysmal nocturnal hemoglobinuria |
| Other inherited thrombophilic conditions: protein C or protein S deficiency, antiphospholipid syndrome, factor V Leyden deficiency, prothrombin gene mutation, antithrombin deficiency, homocysteinemia, and methyltetrahydrofolate (MTHFR) genotype |
| Pregnancy |
| Oral contraceptive use |
| **Local factors with injury to portal or mesenteric veins** |
| Acute intraabdominal process: pancreatitis, ulcerative colitis, Crohn’s disease, diverticulitis, cholecystitis, and appendicitis |

| |
|---|
| Intraabdominal surgery: cholecystectomy, colectomy, LT, splenectomy, portosystemic shunting, and TIPS shunt |
| Abdominal trauma |
| **Sluggish blood flow** |
| Cirrhosis |
| Congestive heart failure |

The prevalence of PVT in patients with cirrhosis varies from 1% to 20% depending on disease severity[34]. The prevalence also varies based on the imaging modality used for diagnosing PVT and the length of follow-up[21] .

Mesenteric vascular disorders include mesenteric arterial ischemia and mesenteric venous thrombosis (MVT). Mesenteric arterial occlusion is mostly due to cardiovascular and embolic causes and will not be discussed. The risk factors for MVT are the same as described for PVT (Table 4). MVT contributes to 10%–20% of all mesenteric vascular ischemic disorders. Although MVT may occur independently of PVT, more often it results from extension of PVT into the mesenteric veins, given the continuity of the portal vein with the mesenteric veins[35,36] .

**Key concepts**

- Investigation for thrombophilia should be performed for portal and/or mesenteric vein thrombosis among patients without cirrhosis in the absence of obvious etiology such as an acute intraabdominal process. In cirrhotic patients, thrombophilia work-up is performed among patients with portal and/or mesenteric vein thrombosis when there is previous history of thrombosis, thrombosis at unusual sites, and family history of thrombosis.
- JAK2 mutation testing should be obtained for evaluation of underlying myeloproliferative neoplasms.

**Clinical features**

Without cirrhosis, acute thrombosis can involve variable extents of the portal vein and presents with acute abdominal pain, often located in the upper abdomen. Fever is also a common symptom and raises suspicion for an acute intraabdominal process such as pyelphlebitis (septic thrombosis of the portal vein). Other PVT features include abdominal distention, nausea, and splenomegaly[37]. PVT in cirrhotic patients may also be due to HCC with malignant infiltration into the portal vein.

PVT may resolve with complete recanalization. Evolution into a chronic thrombus is possible. Development of periportal collaterals (portal cavernoma), PH, and portosystemic collaterals can have serious consequences[37]. PVT in cirrhotic patients

may be associated with worsening PH and/or hepatic decompensation. Prophylactic anticoagulation use in cirrhotic patients for PVT prevention remains controversial[38].

Independent of cirrhosis, abdominal pain is the most common presentation of acute MVT. Other symptoms include nausea, vomiting, fever, anorexia, and jaundice[37,39]. The development of fever, abdominal tenderness, ascites, absence of bowel sounds, and laboratory abnormalities such as leukocytosis or increasing lactate levels should raise the suspicion for compromise of intestinal circulation[39,40]. Patients with chronic MVT may present with PH complications, esophageal and/or gastric varices, and variceal hemorrhage.

**Diagnosis**

Diagnosis of PVT can be done with imaging of the liver and its vasculature. Doppler ultrasound (US) may demonstrate hyperechoic material within the vessel lumen, dilatation of the portal vein, and diminished portal venous flow[37,41]. Ultrasound has a sensitivity of 73%–93%, specificity of 99%, positive predictive value of 86%–97%, and negative predictive value of 98%[32,37]. Corresponding figures for the accuracy of CT scans to diagnose PVT are 90%, 99%, 99%, and 95%, respectively[37]. Advantages of US over CT include lower cost, wider availability, and lack of radiation[37]. CT is more accurate in making a diagnosis of PVT extension. A central lucency within an expanded and sharply defined vein on contrast, cross-sectional imaging suggests an acute PVT. A tumor thrombus related to HCC is recognized by arterialization of the thrombus. In chronic PVT or cavernomatous transformation of the portal vein, the portal vein is not defined, being replaced by collaterals. The presence of portal cavernoma and features of PH including portosystemic collaterals, splenomegaly, and esophageal varices suggest chronic PVT. Portal cavernoma usually appears as serpiginous structures in the area of portal vein, with nonvisualization of the main portal vein[42]. Contrast-enhanced CT scan of the abdomen is 90% accurate in MVT diagnosis. Associated thickened bowel wall and mesentery, indistinct bowel wall margins, and ascites raise suspicion for intestinal infarction or gangrene[43]. MRI is an alternative to CT scans. MR angiography (MRA) can be performed like CT angiography (CTA).

**Key concepts**

- Abdominal pain disproportionate to physical findings on abdominal examination should raise suspicion for portal and/or MVT.
- Intestinal ischemia is suspected with the development of fever, ascites, rebound abdominal tenderness, leukocytosis, and elevated serum lactate levels.
- Hepatic doppler ultrasound should be obtained in patients with new diagnosis of cirrhosis, onset of PH, or hepatic decompensation.

- In chronic PVT, endoscopic evaluation should be performed to assess for esophageal and/or gastric varices.
- Prophylactic anticoagulation for PVT prevention in cirrhosis remains controversial.

**Recommendations**

- Doppler ultrasound examination is recommended as the initial noninvasive modality. Contrast-enhanced CT or MRI scan is recommended to assess the extension of thrombus and to exclude tumor thrombus (strong recommendation, very low level of evidence).

**Treatment**

Management of PVT and MVT in the presence or absence of cirrhosis is discussed separately. Cirrhosis is an independent risk factor for thrombosis with a higher prevalence of PVT. Cirrhosis impacts both procoagulant and anticoagulant factors. Management of PVT and MVT revolves around the use of anticoagulation and prevention of variceal bleeding. In the absence of hemodynamically significant bleeding, anticoagulation is initiated with infusions of unfractionated heparin or subcutaneous administration of LMWH. Anticoagulation is delayed in patients with active bleeding. Maintenance can be achieved with oral anticoagulants or LMWH[44].

**Table 5.** Advantages and Disadvantages of Unfractionated Heparin (UFH) Infusion and Low-Molecular Weight Heparin (LMWH) for Initiating Anticoagulation

| | UFH | LMWH |
|---|---|---|
| **Administration** | Intravenous | Subcutaneous |
| **Frequency** | Infusion | Twice daily |
| **Half-life** | Minutes to 1-2 hours | 6-12 hours |
| **Monitoring** | Needed with activated partial thromboplastin time (aPTT) or Xa | Not needed |
| **Renal function** | No dose change needed | Contraindicated in renal failure and on dialysis |
| **Efficacy** | ++ | +++ |
| **Heparin-induced thrombocytopenia** | +++ | ++ |

**Table 6**. Advantages and Disadvantages of LMWH, VKAs, or DOACs for Maintaining Anticoagulation

| | LMWH | VKA | DOAC |
|---|---|---|---|
| **Administration** | Subcutaneous | Oral | Oral |
| **Frequency** | Twice daily | Once daily | Once or twice daily |
| **Efficacy** | Better in malignancy | ++ | ++ |
| **Renal function** | Contraindicated in renal failure | No dose change | Requires dose modifications |
| **Absorption** | Not affected | Affected from bowel edema in portal hypertension | Affected from bowel edema in portal hypertension |
| **Monitoring** | Not needed | Needed with PT/INR | Probably not needed |
| **Antidote** | Available | Available | Available |

**Portal or mesenteric vein thrombosis in the absence of cirrhosis**

Anticoagulation stops clot propagation and restores vein lumen patency. Anticoagulation is the first-line therapy for patients with symptomatic acute MVT[45,46]. Anticoagulation is given for a finite duration of 3–6 months among patients with reversible etiologies such as acute intraabdominal process or trauma. Indefinite anticoagulation is required for patients with inherited or acquired thrombophilia[47].

Patients with mesenteric vein thrombosis, who have progressive thrombosis despite anticoagulation and are at risk of intestinal ischemia, may be considered for thrombolytic therapy. Patients with suspected or confirmed intestinal infarction or gangrene are treated with surgical resection of the compromised bowel. Bowel viability is determined at the time of surgery[44].

Retrospective studies have demonstrated a lower risk of variceal bleeding in patients with chronic PVT who receive anticoagulation and are maintained on beta-blockers[42].

Beta-blockers are considered the first choice for primary prevention of variceal bleeding. Band ligation should be considered if patients have any contraindication to beta-blockers or do not tolerate these drugs[47].

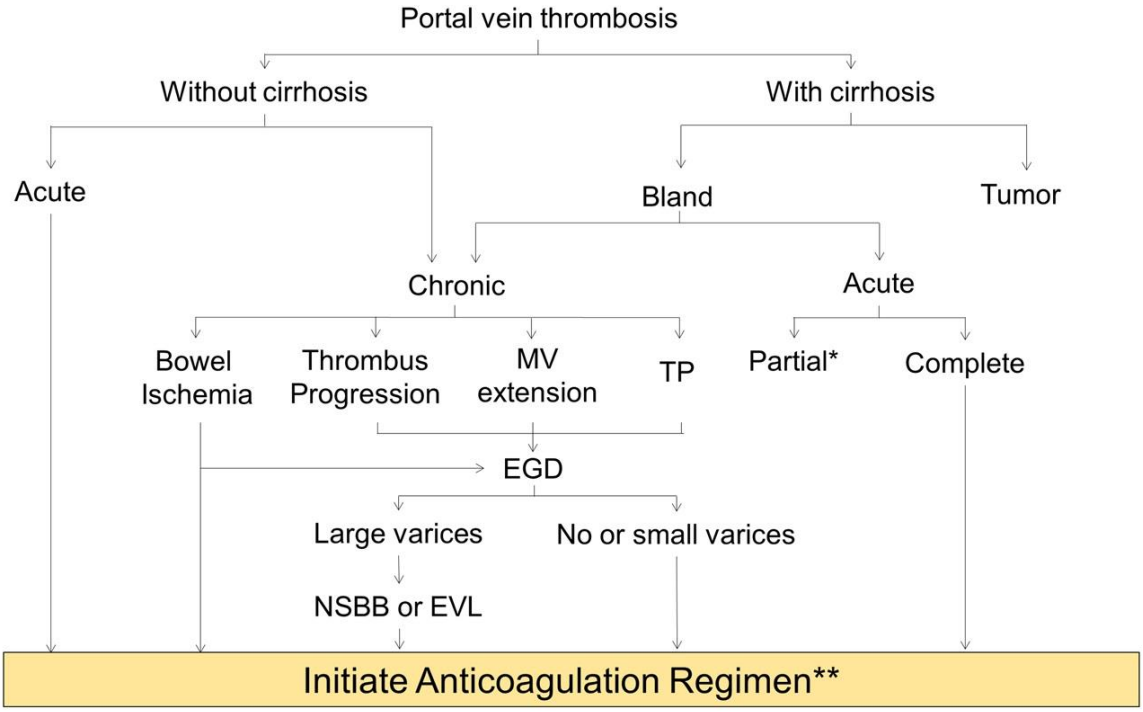
**Recommendations**

- Anticoagulation is recommended for all noncirrhotic patients with acute symptomatic portal or mesenteric vein thrombosis in the absence of any contraindication (strong recommendation, low level of evidence).
- Anticoagulation is suggested for patients with chronic PVT if there is evidence of inherited or acquired thrombophilia, progression of thrombus into the mesenteric veins, or current or previous evidence of bowel ischemia (conditional recommendation, very low level of evidence).
- 6 months of anticoagulation are suggested in patients with portal or mesenteric vein thrombosis without a demonstrable thrombophilia and when the etiology of the thrombosis is reversible. Indefinite anticoagulation is recommended in patients with portal or mesenteric vein thrombosis and thrombophilia (conditional recommendation, very low level of evidence).
- Nonselective beta-blockers are recommended for prevention of variceal bleeding in patients with high-risk varices and portal and/or mesenteric vein thrombosis requiring anticoagulation. Endoscopic variceal ligation may be performed if there are contraindications or intolerance to beta-blockers; however, anticoagulation may need to be interrupted in the periprocedural period (strong recommendation, low quality of evidence).
- Either unfractionated heparin or LMWH are suggested to be used once a decision is made to initiate anticoagulation for treatment of portal and/or MVT. However, pros and cons of either approach should be considered before initiating either regimen (conditional recommendation, very low level of evidence).
- Either LMWH or warfarin may be used. Although this field continues to evolve, there is currently only limited experience with DOAC, which includes Xa or thrombin inhibitors. Because absorption of these agents may be limited in the presence of intestinal edema, some monitoring of therapy is recommended. A normal thrombin time and aPTT for dabigatran and a normal prothrombin time or anti-Xa activity for apixaban and rivaroxaban rule out substantial drug effect. Pros and cons of all approaches including availability of reversal agents should be considered before deciding on the specific regimen (conditional recommendation, very low level of evidence).

**Portal or mesenteric vein thrombosis with cirrhosis**

Anticoagulation as compared to no treatment in cirrhotic patients resulted in higher rates of portal vein patency and lower risk of variceal bleeding or worsening of hepatic dysfunction. Patients with sequela of PH may also be considered for transjugular intrahepatic portosystemic shunt (TIPS)[48]. In complete PVT, direct

transhepatic or transsplenic approach may be attempted[49]. Whether asymptomatic cirrhotic patients with acute PVT who are not candidates for LT should be treated with anticoagulation remains controversial[21,50]. Patients with tumor thrombus from HCC are best managed as per the current evidence and HCC guidelines[51].




*TP: Thrombophilia; EVL: Endoscopic variceal ligation; NSBB: Nonselective Beta-blockers*
**No anticoagulation except for acute partial thrombosis among liver transplant listed candidates*
***Anticoagulation duration: 3-6 months if discrete precipitant and indefinite if thrombophilia or patients listed for liver transplantation*

***Figure 1.*** *Approach to management of portal vein thrombosis (retrieved from the ACG 2020 guidelines)*

PVT among patients listed for LT does not affect mortality. However, complete thrombosis of the PV at the time of LT may worsen post-transplant survival[52]. In cirrhotic patients listed for transplant, anticoagulation should ideally be continued until the time of transplant.

**Key concepts**

- Anticoagulation among cirrhotic patients and portal and/or mesenteric vein thrombosis is not associated with increased risk of variceal bleeding.

**Recommendations**

- We recommend anticoagulation for patients with acute complete main PVT, MVT, or extension of portal venous thrombosis into mesenteric veins. Risk of bleeding must be weighed against benefits as, e.g. in patients with platelets

<50,000/μL or hepatic encephalopathy at risk of falls (strong recommendation, low level of evidence).

- We suggest anticoagulation in patients with chronic PVT only if there is evidence of inherited thrombophilia, progression of thrombus, or history of bowel ischemia due to thrombus extension into the mesenteric veins. Anticoagulation may also be considered in patients awaiting LT (conditional recommendation, very low level of evidence).
- We suggest 6 months of anticoagulation in patients with cirrhosis and acute portal or MVT. Anticoagulation is continued beyond this period in patients with portal or mesenteric vein thrombosis who are on the waiting list for liver transplant (conditional recommendation, very low level of evidence).
- We recommend nonselective beta-blockers for primary prevention of variceal bleeding in cirrhotic patients with high-risk varices and portal and/or mesenteric vein thrombosis requiring anticoagulation. Endoscopic variceal ligation may be performed if there is a contraindication to or intolerance to beta-blockers; however, anticoagulation may need to be interrupted in the periprocedural period (strong recommendation, low quality of evidence).
- We suggest either unfractionated heparin or LMWH for treatment of portal and/or MVT once a decision is made to initiate anticoagulation. Unfractionated heparin is preferred in the presence of renal insufficiency, and LMWH is preferred in the presence of thrombocytopenia (conditional recommendation, very low level of evidence).

**Portal hypertensive or portal cavernoma cholangiopathy**

Portosystemic collaterals around the common bile duct in patients with chronic PVT can be associated with common bile duct obstruction. This results in cholangiopathy, termed portal hypertensive cholangiopathy[53]. Patients may present with symptoms of cholestasis including pruritus. These patients are also at risk of developing bacterial cholangitis and intraductal stones[53].

Diagnosis requires presence of a cholestatic liver chemistry profile, portal cavernoma, extrahepatic biliary abnormalities on imaging, and absence of any other etiology to explain the cholangiographic abnormalities[53]. MR cholangiogram (MRCP) is used to make the diagnosis. Endoscopic retrograde is required for removal of intraductal stones and/or placement of biliary stents. Portal decompression with a surgical shunt is considered in patients who are refractory to endoscopic intervention[54]. Rarely, biliary decompression may require a surgical approach with Roux-en-Y hepaticojejunostomy[54] .

**Key concepts**

- Endoscopic treatment of portal hypertensive cholangiopathy is indicated among symptomatic patients with cholangitis. Patients with choledocholithiasis or biliary stricture may also benefit from endoscopic treatment. Surgical intervention when technically feasible should only be considered in the rare situation when endoscopic interventions are ineffective.

## 1.3 European Guidelines

### 1.3.1 European Association for the Study of the Liver (EASL) Clinical Practice Guidelines on Prevention and Management of Bleeding and Thrombosis in Patients with Cirrhosis (2022)

The European Association for the Study of the Liver (EASL) published its clinical guidelines for the prevention and management of thrombosis in patients with cirrhosis in the Journal of Hepatology in 2022[55]. A summary of the recommendations can be found below:

- In patients with cirrhosis and abnormal laboratory tests (INR, Activated Partial Thromboplastin Time (APTT), platelet count, fibrinogen), attempting to correct these tests by administering blood products or factor concentrates, with the aim of preventing spontaneous bleeding, is not recommended (LoE 3, strong recommendation).
- INR and APTT do not predict post-procedural bleeding in patients with cirrhosis undergoing invasive procedures (LoE 3).
- Studies do not consistently demonstrate a link between thrombocytopenia, hypofibrinogenaemia, or viscoelastic test results and the risk of post-procedural bleeding, although there may be subgroups in whom thrombocytopenia is related to procedural bleeding risk and there is initial evidence suggesting that viscoelastic tests might help to address this issue (LoE 4).
- In patients with cirrhosis, the use of traditional hemostasis tests, or viscoelastic tests, cannot be generally indicated to predict procedural bleeding risk, although they can be used to assess severity of disease or hemostatic status and to provide an initial benchmark to guide management in the case of post-procedural bleeding (LoE 3, strong recommendation).
- In patients with cirrhosis undergoing invasive procedures with a low risk of bleeding, laboratory evaluation of hemostasis with the aim of predicting post-procedural bleeding is not indicated (LoE 4, strong recommendation).

- There is weak evidence that the measurement of platelet count might be indicated to identify patients at increased procedural bleeding risk. No solid data are available for fibrinogen (LoE 4).
- As evidence supporting viscoelastic tests as predictors of procedure-related bleeding in patients with acute decompensation of cirrhosis, with or without organ failure, is weak, it is not possible to advise for or against their use (LoE 4).
- In patients with cirrhosis undergoing invasive procedures associated with a high risk of bleeding, laboratory evaluation of hemostasis is generally not indicated to predict post-procedural bleeding, although it may serve to provide a baseline status of the patient and to assist the physician in the case of bleeding events (LoE 4/5, weak recommendation).
- In patients with cirrhosis undergoing invasive procedures, correction of a prolonged INR with FFP is not recommended to decrease the rate of procedure-related clinically relevant bleeding (LoE 1, strong recommendation).
- In patients with cirrhosis undergoing invasive procedures, routine use of Prothrombin Complex Concentrates (PCCs) to decrease the rate of procedure-related clinically relevant bleeding is discouraged (LoE 3, weak recommendation).
- In patients with cirrhosis undergoing invasive procedures, no studies have specifically evaluated whether the infusion of platelet concentrates, or thrombopoietin receptor (TPO-R) agonists decrease the rate of procedure-related clinically relevant bleeding (LoE 1).
- In patients with cirrhosis undergoing invasive procedures, infusion of platelet concentrates, or use of TPO-R agonists is not recommended when platelet count is above 50 × 109/L or when bleeding can be treated by local hemostasis (LoE 3/4, strong recommendation).
- In patients undergoing high-risk procedures in whom local hemostasis is not possible and platelet count is between 20 × $10^9$ /L and 50 × $10^9$ /L infusion of platelet concentrates, or TPO-R agonists should not be routinely performed but may be considered on a case-by-case basis (LoE 3/4, strong recommendation).
- In patients undergoing high-risk procedures in whom local hemostasis is not possible and platelet count is very low (<20 x $10^9$ /L) **infusion of platelet concentrates** or **TPO-R agonists** should be considered on a case-by-case basis (LoE 3/4, strong recommendation).

- In patients with cirrhosis undergoing invasive procedures, routine correction of fibrinogen deficiency to decrease the rate of procedure-related clinically relevant bleeding is discouraged (LoE 5, strong recommendation).
- In patients with cirrhosis, every effort should be made to optimize hemoglobin levels by treating **iron**, **folic acid**, **vitamin B6**, and **vitamin B12** deficiencies, especially in those patients likely to undergo invasive procedures (LoE 5, weak recommendation).
- In the setting of invasive procedures, prophylactic red blood cell transfusion with the aim of decreasing the risk of procedure-related bleeding is not recommended (LoE 5, weak recommendation).
- In patients with cirrhosis undergoing invasive procedures, routine use of tranexamic acid to decrease the rate of procedure-related clinically relevant bleeding is discouraged (LoE 4, weak recommendation).
- In patients with stable cirrhosis and abnormal laboratory tests (prothrombin time, APTT, platelet count, fibrinogen) undergoing prophylactic band ligation, administration of blood products or factor concentrates with the aim of avoiding post-ligation bleeding is not recommended (LoE 5, strong recommendation).
- In patients with cirrhosis, **antiplatelet** and/or **anticoagulant agents** should be managed following the same guidelines as in patients without cirrhosis before invasive procedures (LoE 4, strong recommendation).
- In patients with cirrhosis, imaging guidance is recommended for liver biopsy, central venous line placement and jugular puncture for Trans-jugular Intrahepatic Portosystemic Shunt (TIPS) placement (LoE 3, strong recommendation).
- Patients with cirrhosis undergoing invasive procedures should be monitored for bleeding complications in the same way as patients without cirrhosis (LoE 3, strong recommendation).
- In patients with cirrhosis and active variceal bleeding, if hemostasis is achieved with portal hypertension-lowering drugs and endoscopic treatment, correction of hemostatic abnormalities is not indicated (LoE 3, strong recommendation). In case of failure to control hemorrhage, the decision to correct hemostasis should be considered on a case-by-case basis (LoE 3, strong recommendation).
- In patients with cirrhosis and active variceal bleeding, tranexamic acid should not be used (LoE 2, strong recommendation).

- No studies evaluating correction of hemostasis in patients with cirrhosis and active bleeding related to portal hypertension, but not to varices (e.g., portal hypertensive gastropathy), are available (LoE 5).
- In patients with cirrhosis and active bleeding related to portal hypertension, but not to varices (e.g., portal hypertensive gastropathy), bleeding should be managed with portal hypertension-lowering measures (LoE 5, weak recommendation).
- In the case of failure to control hemorrhage with portal hypertension-lowering drugs, the decision to correct hemostasis should be considered on a case-by-case basis (LoE 5, weak recommendation).
- In patients with cirrhosis who are actively bleeding from a non-portal hypertensive cause, active bleeding should first be addressed by local measures and/or interventional radiology procedures (LoE 4, strong recommendation). In those patients in whom local measures fail to stop the bleeding, addressing contributing factors (renal failure, infection or sepsis, and anemia) may reduce bleeding while correction of hemostatic abnormalities can be considered on a case-by-case basis (LoE 5, weak recommendation).
- In patients with cirrhosis, routine use of antifibrinolytic agents to treat active bleeding from a non-portal hypertension-related cause is discouraged (LoE 5, weak recommendation).
- There is initial evidence that the use of viscoelastic tests is associated with decreased blood product use in patients with cirrhosis and active upper gastrointestinal bleeds, without differences in bleeding control and mortality (LoE 3). Given the benefits of reducing blood transfusion, viscoelastic tests can be used when available (LoE 1, strong recommendation).
- The use of viscoelastic tests or other laboratory tests to identify which patients with cirrhosis are at risk of venous thromboembolism (VTE), Deep Vein Thrombosis/Pulmonary Embolism (DVT/PE) is not recommended (LoE 5, strong recommendation).
- In patients with cirrhosis at risk of DVT/PE, thromboprophylaxis with **LMWH** can be recommended as it has a reasonable safety profile, but efficacy is unclear based on available data (LoE 3, weak recommendation).
- In patients with Child-Pugh class A and B cirrhosis at risk of DVT/PE, thromboprophylaxis with **DOACs** can be recommended as DOACs have a reasonable safety profile in these patients, but efficacy data are still limited.
- In patients with Child-Pugh C cirrhosis, DOACs are not recommended (Safety: LoE 2; Efficacy: LoE 4; weak recommendations).

- For treatment of DVT/PE, **VKA** should be used with caution in patients with cirrhosis, as these patients can have baseline altered INR and thus target INR remains unknown. In patients with Child-Pugh A, LMWH, and VKA are reasonable options. Until more data become available, we recommend LMWH for treatment of DVT/PE in patients with Child-Pugh B and Child-Pugh C cirrhosis, whereas **UFH** is the treatment of choice in case of renal failure (LoE 4, weak recommendation).
- For the treatment of DVT/PE in patients with cirrhosis, currently available data suggest that there are no major concerns regarding the safety of DOACs in patients with Child-Pugh class A cirrhosis. Due to the possibility of accumulation, DOACs should be used with caution in Child-Pugh class B patients, as well as in patients with creatinine clearance below 30 ml/min. The use of DOACs in Child-Pugh class C patients is not recommended (LoE 4, strong recommendation).

## 1.4 International Guidelines

### 1.4.1 Chinese Consensus for Management of Portal Vein Thrombosis in Liver Cirrhosis (2020)

The Hepatobiliary Disease Study Group, Chinese Society of Gastroenterology, Chinese Medical Association published their clinical guidelines for the management of portal vein thrombosis in liver cirrhosis in the Journal of Digestive Diseases in 2020[56]. *The following guideline does not provide a specified grade of evidence or level of recommendation*:

**Diagnosis and differential diagnosis of PVT in liver cirrhosis**

PVT in liver cirrhosis can be diagnosed based on the history of chronic liver disease and typical imaging characteristics. Liver biopsy should be performed when imaging examination shows the presence of PVT but without sufficient evidence for cirrhosis. Cirrhotic PVT should be differentiated from noncirrhotic PVT and portal vein tumor thrombosis based on a combination of biochemical indicators, serum α-fetoprotein levels, imaging characteristics, and pathological findings.

**Assessment of PVT in liver cirrhosis**

1. **Staging**

Staging of PVT is critical for the establishment of subsequent antithrombotic therapeutic strategy. PVT in liver cirrhosis is mainly identified accidentally during routine imaging examination for the assessment of the severity of liver cirrhosis or liver cancer surveillance. Therefore, it is often difficult to accurately determine the

time of onset of PVT. Thus, classifying acute and chronic cirrhotic PVT based on the timing of the disease onset is not recommended. Instead, such classification is recommended to be performed based on PVT-related clinical manifestations. Acute symptomatic PVT is considered when a patient with liver cirrhosis manifests acute abdominal pain (symptoms and signs may be inconsistent at the disease onset), nausea, and vomiting, etc; otherwise, non-acute symptomatic PVT should be considered. In clinical practice, when acute abdominal pain lasts for over 24 hours in a cirrhotic patient regardless of fever or intestinal obstruction, acute symptomatic PVT should be highly suspected and imaging examinations are needed to confirm the diagnosis. If a cirrhotic patient presents with fever and chill with or without abdominal infection, blood culture should be routinely performed.

2. **Grade**

The Yerdel classification, which is currently the most commonly used system for grading PVT, includes the following:

a. thrombus occlusion of less than 50% of the portal vein, with or without minimal extension of the mesenteric vein;

b. thrombus occlusion of more than 50% of the portal vein, including complete thrombosis, with or without minimal extension of the mesenteric vein;

c. complete thrombosis of the portal vein and proximal mesenteric vein;

d. complete thrombosis of the portal vein and proximal and distal mesenteric veins.

Notably, the Yerdel classification is proposed to predict primarily the technical complexity and risk of post-operative complications before liver transplantation, but its role in the selection of antithrombotic strategy still needs to be clarified.

The Baveno VI consensus has also proposed a grading system for PVT. However, this grading system is not designed particularly for PVT in liver cirrhosis, but involves nearly all conditions related to PVT, such as malignant, non-cirrhotic, and post-transplant PVT.

Currently, PVT in liver cirrhosis is classified as **mural**, **partial**, and **complete obstruction**, and **fibrotic cord**, which seems to be more convenient and helpful to guide clinical decisions. Mural PVT refers to thrombus occlusion of less than 50% of the portal vein. Complete PVT refers to complete thrombosis of the portal vein. Partial PVT refers to the grade of thrombosis between mural and complete PVT. And fibrotic cord refers to the portal vein completely obliterated and organized, in which the lumen of the portal vein cannot be identified by imaging examination. Portal cavernoma can be frequently observed in cases of complete PVT and fibrotic cord.

### 3. Evolution

Development and progression of PVT in liver cirrhosis should be dynamically evaluated to modify the treatment strategy in a timely fashion. Definition of changes of cirrhotic PVT is important for the standardization of the end-points in future studies. According to the development and changes in the grade of PVT, the evolution of cirrhotic PVT is defined as follows.

- New-onset PVT refers to the development of de novo PVT in the absence of thrombosis on prior imaging examination.
- Partial recanalization refers to the improvement of severity of persistent PVT by no less than one grade.
- Complete recanalization refers to the disappearance of prior PVT.
- Progression refers to the deterioration of severity of persistent PVT by no less than one grade.
- Stability refers to the persistence of prior PVT without any change of PVT grade; while recurrence refers to recurrent thrombus after the disappearance of prior PVT.

**Stepwise treatment strategy of PVT in liver cirrhosis**

When deciding whether and when to start treatment for cirrhotic PVT and what treatment strategy is to be used, the stage, grade, extension and changes of PVT, clinical manifestations, complications of portal hypertension, and risk of bleeding need to be considered.

A preliminary stepwise treatment strategy of PVT in liver cirrhosis has been proposed by the present consensus (**Figure 2**).

Acute symptomatic PVT should be treated with **antithrombotic agents** in a timely fashion to recanalize the portal vein and prevent thrombus extension.

If anti-thrombotic therapy is ineffective for acute symptomatic PVT, and intestinal ischemia and necrosis develop, surgeons should be actively consulted to identify the necessity and feasibility of surgery. Gastro-esophageal variceal bleeding or high-risk GEV should be treated before anticoagulation therapy.

TIPS should be considered for cirrhotic patients with PVT who still suffer recurrent gastroesophageal variceal bleeding after conventional pharmacological and endoscopic therapy.

A “wait-and-see” strategy can be employed for mural PVT without involvement of mesenteric veins, since some of them may spontaneously improve or even disappear without anticoagulation therapy; while PVT may progress in others, necessitating the use of anticoagulation therapy. Additionally, anticoagulation

therapy should be given to patients with partial PVT with involvement of mesenteric vein.

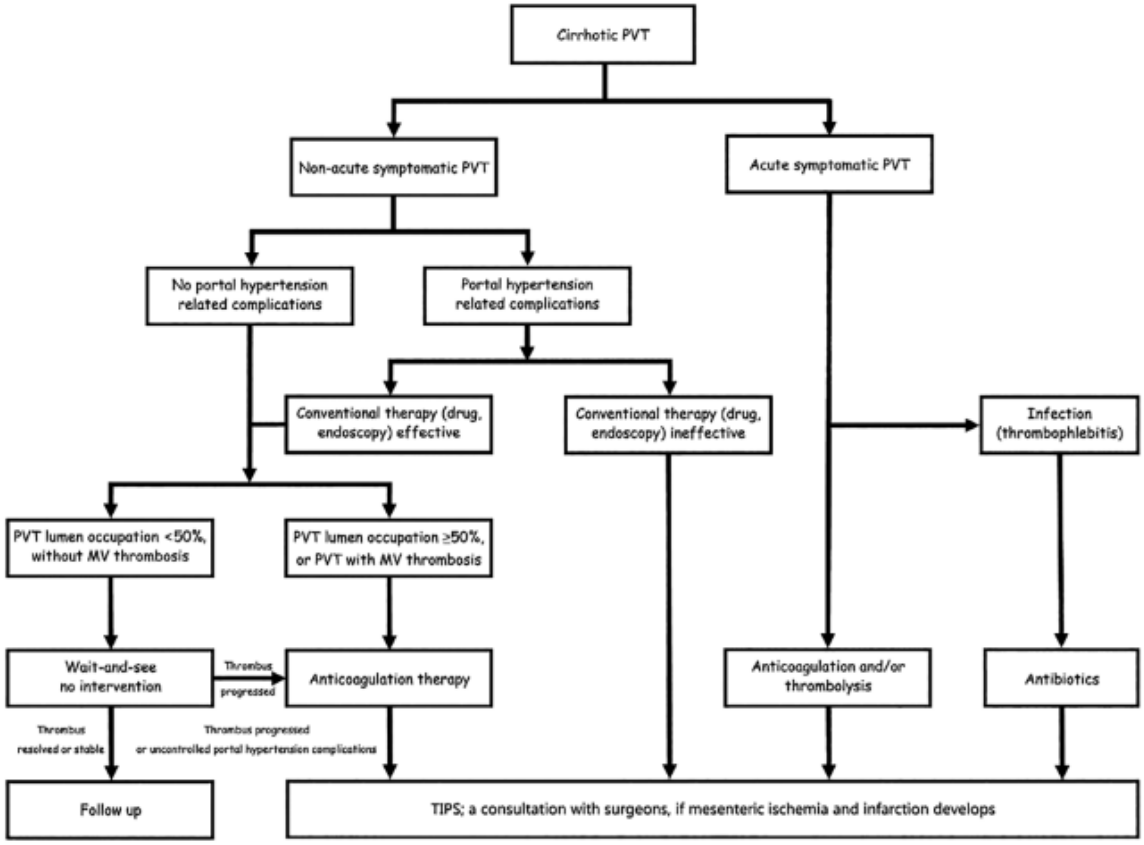



***Figure 2**. A stepwise treatment strategy of cirrhotic PVT (retrieved from the Chinese 2020 guidelines)*

### Treatment for PVT in liver cirrhosis

The mainstay treatment for cirrhotic PVT includes **anticoagulation**, **thrombolysis**, and **TIPS**. In some cirrhotic patients with PVT, thrombosis will be spontaneously recanalized without the use of antithrombotic therapy or other interventional vascular therapy, which is termed transient PVT in liver cirrhosis. However, it is still difficult to identify such patients or to define the interval of follow-up imaging examinations. On the other hand, a higher recanalization rate of PVT is positively associated with a shorter interval between the diagnosis of PVT and initiation of anticoagulation therapy. Therefore, the optimal timing of treatment for PVT should be further explored in more studies.

## 1. Anticoagulation

Major indications for anticoagulation therapy include acute symptomatic PVT, candidates for liver transplantation, and thrombosis extension into the mesenteric veins. However, anticoagulation therapy should be postponed for patients with a recent history of bleeding, high-risk GEV, and severe thrombocytopenia.

Endoscopic examination and blood coagulation test should be performed to evaluate the risk of bleeding before initiation of anticoagulation for PVT in cirrhosis.

Before anticoagulation therapy, nonselective β-blockers and/or endoscopic variceal therapy should be considered as the primary prophylaxis of variceal bleeding in patients with cirrhotic PVT and high-risk GEV. Before anticoagulation therapy, nonselective β-blocker combined with endoscopic variceal therapy should be considered as the secondary prophylaxis of variceal bleeding in patients with cirrhotic PVT and a previous history of gastroesophageal variceal bleeding.

Indications and contraindications for anticoagulation therapy

Anticoagulation therapy for cirrhotic PVT should be individualized. Major indications for anticoagulation therapy include acute symptomatic PVT, candidates for liver transplantation, and thrombosis extension into the mesenteric veins. Major contraindications for anticoagulation therapy often include recent history of bleeding, high-risk GEV, and severe thrombocytopenia. However, the cut-off value of severe thrombocytopenia remains controversial. Anticoagulation therapy should be cautiously given in patients with advanced liver cirrhosis, especially those with Child–Pugh C cirrhosis.

Types of anticoagulants

**LMWH and DOACs are relatively safe and effective in patients with compensated liver cirrhosis and PVT. But the safety and efficacy of DOACs in cirrhotic patients with Child–Pugh C cirrhosis need further evaluation.**

- Anticoagulants include VKA, heparins, and DOACs. Warfarin is a major type of VKA. The therapeutic dosage of warfarin can be achieved with close monitoring of INR. Traditionally, the level of INR should be elevated to 2–3 × Upper Limit of Normal (ULN). Notably, INR is often high in patients with end-stage liver disease in the absence of warfarin use. Therefore, how to accurately monitor the use of warfarin in patients with liver cirrhosis is still uncertain. In addition, the INR may easily be influenced by food and drugs, which further increases the difficulty in assessing the efficacy of warfarin.
- Heparins mainly include UFH, LMWH, and fondaparinux. The therapeutic dose of UFH can be achieved with close monitoring of activated partial thromboplastin time (APTT). Traditionally, the level of APTT should increase to

1.5–2.5 × ULN. Notably, heparin-induced thrombocytopenia (HIT) often occurs within 5 days after the use of unfractionated heparin.

- Therefore, it has been recommended that platelet count should be monitored within 3–10 days after the use of UFH. **LMWH** leads to a lower risk of HIT and bleeding compared with UFH. Therefore, it is often unnecessary to monitor platelet count in patients receiving LMWH, while LMWH should be used with caution in those with renal insufficiency.
- Because LMWH needs to be injected subcutaneously, LMWH followed by oral anticoagulants can be given to patients with a poor compliance to the medication.
- 1-month subcutaneous injection of nadroparin calcium followed by 5-month oral administration of warfarin is effective and safe.
- **Fondaparinux** has been reported to successfully recanalize PVT in seven patients with decompensated liver cirrhosis without bleeding complication or HIT.
- New DOACs include **direct factor Xa inhibitors** (ie, **rivaroxaban** and **apixaban**) and **direct factor IIa inhibitors** (ie, **dabigatran**). The safety and effectiveness of direct oral anticoagulants may be superior to those of traditional anticoagulants. Direct factor Xa inhibitors can be safely given to patients with mild and moderate renal dysfunction.
- The most commonly used type of direct oral anticoagulants was rivaroxaban, followed by dabigatran and apixaban, and that the selection of direct oral anticoagulants was primarily due to no need of monitoring INR.
- Rivaroxaban is superior to warfarin for patients with liver disease-related PVT, but should be cautiously interpreted because of the limitation in patient selection. It should be noted that rivaroxaban, which is mainly metabolized by the liver, is suitable for Child–Pugh A cirrhotic patients, but should be used with caution for those with Child–Pugh B or C cirrhosis.

Dosage of anticoagulants

The Chinese practice guideline for management of deep vein thrombosis recommended subcutaneous injection of LMWH at 100 U/kg every 12 hours. The dosage of LWMH for cirrhotic PVT differ among studies, including nadroparin 5700 UI/day, nadroparin 85 IU/kg every 12 hours, and enoxaparin 200 $U/kg.d^{-1}$ .

There was no significant difference in the rates of portal vein recanalization and variceal bleeding in cirrhotic PVT between enoxaparin 1 mg/kg every 12 hours and enoxaparin 1.5 mg/kg per day, while a dose of 1.5 mg/kg per day led to a higher risk of nonvariceal bleeding. By comparison, rivaroxaban can often be administered at a

fixed dose, with no need to adjust the dose according to the diet, body weight, and mild liver and kidney damage.

Duration of anticoagulants

**Long-term anticoagulation therapy should be considered in patients with mesenteric vein thrombosis or previous history of intestinal ischemia and necrosis, candidates for liver transplantation, and those with hereditary thrombophilia.**

The Baveno VI consensus and the European Association for the Study of the Liver (EASL) clinical practice guideline recommend the followings:

a. duration of anticoagulation therapy should be more than 6 months;
b. anticoagulation therapy should be maintained for several months after complete portal vein recanalization or until liver transplantation;
c. long-term anticoagulation therapy should be considered in patients with mesenteric vein thrombosis or history of intestinal ischemia and necrosis, candidates for liver transplantation, or those with hereditary thrombophilia.

Six-month anticoagulation therapy may be insufficient to achieve portal vein recanalization in some cirrhotic patients with PVT; for such patients, the duration of anticoagulation should be prolonged to 12 months. Therefore, if portal vein recanalization has not been significantly improved after the first 6-month anticoagulation therapy, an extended anticoagulation protocol to 12 months should be attempted.

Management of bleeding during anticoagulation therapy

If a bleeding event develops during anticoagulation therapy, the use of anticoagulants is recommended to be delayed or discontinued according to the severity of bleeding. Diagnostic and therapeutic endoscopy for gastrointestinal bleeding should be performed as soon as possible. Antagonists should be used for major/ fatal bleeding, and transfusion of red blood cells, fresh-frozen plasma, and platelets should be given as replacement therapy.

**2. Thrombolysis**

- Efficacy and safety of thrombolysis for cirrhotic PVT should be further evaluated by more high-quality studies.
- The contraindications for thrombolysis should be avoided, such as recent history of major surgery and trauma, uncontrolled active bleeding, severe hypertension, and aortic dissection.

- The patient's willingness and physical condition should be assessed, such as age, nutritional status, liver and kidney functions, as well as blood coagulation function.
- The indications for thrombolysis should be considered.
- The optimal indication for thrombolytic therapy is acute symptomatic PVT with an elevated D-dimer level.
- Notably, thrombolytic therapy is not indicated for either fibrotic cord or extensive portal cavernoma.
- There are two major approaches of thrombolysis: local and systemic. Local catheter-directed thrombolysis can be performed via a percutaneous transhepatic, transjugular, or transmesenteric approach. Notably, a percutaneous transhepatic approach should be cautiously employed due to its potential risk of bleeding.
- During thrombolytic therapy, the D-dimer level and coagulation function of the patients should be closely monitored to evaluate the risk of hemorrhagic complications. Portal vein patency should be evaluated at 3–5 days after thrombolytic therapy, and the duration of thrombolytic therapy should be 2 weeks at most.
- A continuous use of anticoagulants after thrombolysis and the duration of anticoagulation should be decided based on portal vein recanalization and the patient's overall condition.

**3. TIPS**

- Indications of TIPS for cirrhotic PVT include poor response to or contraindications for anticoagulation, ineffective conventional therapy for gastroesophageal variceal bleeding, or acute symptomatic PVT accompanied with gastroesophageal variceal bleeding.
- TIPS can accelerate the portal vein inflow, which is beneficial for PVT recanalization. The technical feasibility of TIPS in the settings of PVT has been widely recognized, but it remains technically difficult in patients with extensive obliteration of intrahepatic portal vein branches and fine collateral vessels.
- TIPS should be indicated for cirrhotic PVT if the treatment efficacy of anticoagulation is poor or there is a contraindication for anticoagulation; if conventional therapy is ineffective for gastroesophageal variceal bleeding in cirrhotic patients with PVT; or if acute symptomatic PVT is accompanied with gastroesophageal variceal bleeding.

- The role of early TIPS in cirrhotic patients with high-risk GEV and PVT should be further explored. The efficacy and safety of TIPS for recanalization of PVT in liver cirrhosis have been widely confirmed in China.
- Compared with conventional endoscopy in combination with propranolol and anticoagulation, TIPS can significantly increase the rate of portal vein recanalization and decrease the rate of rebleeding, but without any survival benefit.
- Considering the potential risk of peritoneal bleeding and pulmonary embolism, TIPS should be performed at highly experienced centers. Additionally, it should be recognized that TIPS would increase the technical difficulty of liver transplantation in the future.

# Section 2.0 Drug Therapy

## 2.1 Unfractionated Heparin: Heparin Sodium

Information on Heparin Sodium is detailed in the table below.

**Table 7.** Heparin Sodium Drug Information

| SCIENTIFIC NAME<br>HEPARIN SODIUM | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA Approval** | Yes |
| **US FDA** | Yes; 1939 |
| **EMA** | Yes |
| **MHRA** | Yes |
| **PMDA** | No |
| **Indication (ICD-10)** | I81 |
| **Drug Class** | Antithrombotic agents |
| **Drug Sub-class** | Heparin group |
| **ATC Code** | **C05BA03** |
| **DRUG INFORMATION** | |
| **Dosage Form** | Solution for injection |
| **Route of Administration** | Intravenous use/ Subcutaneous |
| **Dose (Adult) [DDD]*** | **Inpatient treatment: IV: Initial: 80 units/kg bolus followed by a continuous infusion of 18 units/kg/hour or 5,000-unit bolus followed by 1,333 units/hour** |
| **Maximum Daily Dose Adults*** | N/A |
| **Adjustment** | Renal impairment prior to treatment:<br>- No initial dosage adjustment necessary<br>Hepatic impairment prior to treatment:<br>- No dose adjustment required |
| **Prescribing edits*** | N/A |
| **AGE (Age Edit):** MD | |

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|---|---|
| **CU (Concurrent Use Edit):** N/A | |
| **G (Gender Edit):** N/A | |
| **MD (Physician Specialty Edit):** N/A | |
| **PA (Prior Authorization):** N/A | |
| **QL (Quantity Limit):** N/A | |
| **ST (Step Therapy):** N/A | |
| **EU (Emergency Use Only):** N/A | |
| **PE (Protocol Edit):** N/A | |
| **SAFETY** | |
| **Main Adverse Drug Reactions (most common and most serious)** | - Most common: Skin ulceration; Bruise<br>- Most serious: Major bleeding; Thrombocytopenia |
| **Drug Interactions*** | Vitamin K Antagonists (eg, warfarin): Anticoagulants may enhance the anticoagulant effect of Vitamin K Antagonists. (Risk C)<br><br>Thrombolytic Agents: May enhance the anticoagulant effect of Anticoagulants (Risk C)<br><br>**Category X: defibrotide, edoxaban, hemin, mifepristone, omacetaxine, oritavancin, rivaroxaban, streptokinase, telavancin, urokinase.** |
| **Special Population** | Older adult |
| **Pregnancy** | Heparin does not cross the placenta |
| **Lactation** | Heparin is considered acceptable for use in patients who are breastfeeding |
| **Contraindications** | - Hypersensitivity<br>- Severe thrombocytopenia<br>- History of HIT<br>- History of HIT with thrombosis<br>- Uncontrolled active bleeding |
| **Monitoring Requirements** | - Hemoglobin, hematocrit, platelet count, PT, aPTT, signs/symptoms of bleeding, risk factors for bleeding, |

| | |
|---|---|
| | fecal occult blood test<br>- Level of anticoagulation can be monitored by anti-Factor Xa activity or aPTT |
| **Precautions** | - Bleeding risk<br>- Heparin resistance<br>- Hyperkaliemia<br>- Hypersensitivity<br>- Thrombocytopenia |
| **Black Box Warning** | Epidural or spinal hematomas may occur in patients who are anticoagulated with LMWHs or heparinoids and are receiving neuraxial anesthesia or undergoing spinal puncture. |
| **REMS*** | N/A |

## HEALTH TECHNOLOGY ASSESSMENT (HTA)

HTA reviews and recommendations of PVT treatment options are not available by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC).

## CONCLUSION STATEMENT- UFH

**UFH is usually used in the inpatient setting for PVT.** The therapeutic dose of UFH can be achieved with close monitoring of aPTT. Traditionally, the level of aPTT should increase to 1.5–2.5 × ULN. Notably, HIT often occurs within 5 days after the use of unfractionated heparin. Therefore, it has been recommended that platelet count should be monitored within 3–10 days after the use of UFH. **LMWH** leads to a lower risk of HIT and bleeding compared with UFH.

Limitations for the use of UFH include hypersensitivity, history of HIT in the past 100 days and active major bleeding. Platelet count and aPTT should always be monitored.

## 2.2 Low-Molecular Weight Heparin (LMWH): Enoxaparin

Information on Enoxaparin is detailed in the table below.

**Table 8.** Enoxaparin Drug Information

| SCIENTIFIC NAME<br>ENOXAPARIN | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA Approval** | Yes |
| **US FDA** | Yes; December 1998 |
| **EMA** | Yes; December 2016 |
| **MHRA** | Yes |
| **PMDA** | No |
| **Indication (ICD-10)** | I81 |
| **Drug Class** | Antithrombotic agents |
| **Drug Sub-class** | LMWH |
| **ATC Code** | **B01AB05** |
| **DRUG INFORMATION** | |
| **Dosage Form** | Solution for injection in pre-filled syringe |
| **Route of Administration** | Intravenous use/ Subcutaneous |
| **Dose (Adult) [DDD]*** | **SC: 1 mg/kg every 12 hours (preferred) or 1.5 mg/kg once every 24 hours.** |
| **Maximum Daily Dose Adults*** | N/A |
| **Adjustment** | Renal impairment prior to treatment:<br>- CrCl >50 mL/minute: No dose adjustment necessary for most indications.<br>- CrCl 30 to 50 mL/minute: No dose adjustment necessary for most indications.<br>- CrCl <30 mL/minute: 1 mg/kg once daily.<br>Hepatic impairment prior to treatment:<br>- No dose adjustment required |

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| **Prescribing edits*** | N/A |
| **AGE (Age Edit):** N/A | |
| **CU (Concurrent Use Edit):** N/A | |
| **G (Gender Edit):** N/A | |
| **MD (Physician Specialty Edit):** N/A | |
| **PA (Prior Authorization):** N/A | |
| **QL (Quantity Limit):** N/A | |
| **ST (Step Therapy):** N/A | |
| **EU (Emergency Use Only):** N/A | |
| **PE (Protocol Edit):** N/A | |
| **SAFETY** | |
| **Main Adverse Drug Reactions (most common and most serious)** | - Most common: anemia; ecchymosis<br>- Most serious: major bleeding; spinal or epidural hematomas; thrombocytopenia |
| **Drug Interactions*** | Vitamin K Antagonists (e.g., warfarin): Anticoagulants may enhance the anticoagulant effect of Vitamin K Antagonists. (Risk C)<br><br>**Category X**: apixaban, dabigatran, defibrotide, edoxaban, hemin, rivaroxaban, urokinase. |
| **Special Population** | Older adult; low weight patients; elective surgery |
| **Pregnancy** | LMWH does not cross the placenta. Recommended in pregnancy. |
| **Lactation** | It is not known if enoxaparin is present in breast milk. |
| **Contraindications** | - Hypersensitivity<br>- History of HIT in the past 100 days<br>- Active major bleeding |
| **Monitoring Requirements** | - Platelet count, hemoglobin, hematocrit, fecal occult blood, signs and symptoms of bleeding, anti-factor Xa levels (as |

| | |
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| | appropriate), and serum creatinine at baseline and during therapy |
| **Precautions** | - Bleeding risk<br>- Hyperkaliemia<br>- Thrombocytopenia |
| **Black Box Warning** | Epidural or spinal hematomas may occur in patients who are anticoagulated with LMWH or heparinoids and are receiving neuraxial anesthesia or undergoing spinal puncture. |
| **REMS*** | N/A |

## HEALTH TECHNOLOGY ASSESSMENT (HTA)

HTA reviews and recommendations of PVT treatment with enoxaparin are not available by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC).

The table below lists the HTA reviews and recommendations of pulmonary embolism treatment with enoxaparin by these agencies/institutes/authorities.

**Table 9.** Enoxaparin HTA Analysis

| MEDICATION | AGENCY | DATE – HTA RECOMMENDATION |
|---|---|---|
| **Enoxaparin** | NICE | N/A |
| | CADTH | N/A |
| | HAS[57] | Unfavorable opinion for reimbursement of LOVENOX (enoxaparin) in the extended treatment of deep vein thrombosis and pulmonary embolism, and prevention of their recurrence(s) in patients with active cancer. |
| | IQWIG | N/A |
| | PBAC | Pending PBAC outcomes |

**CONCLUSION STATEMENT- Enoxaparin**

**LMWH is relatively safe and effective in patients with compensated liver cirrhosis and PVT.** Because LMWH needs to be injected subcutaneously, LMWH followed by oral anticoagulants can be given to patients with a poor compliance to the medication. It is the drug of choice for pregnant women. An Unfavorable opinion for reimbursement of LOVENOX (enoxaparin) in the extended treatment of pulmonary embolism, and prevention of their recurrence(s) in patients with active cancer was declared by the HAS HTA. Limitations for the use of Enoxaparin include hypersensitivity, history of HIT in the past 100 days and active major bleeding.

## 2.3 Warfarin

Information on Warfarin is detailed in the table below.

**Table 10**. Warfarin Drug Information

| SCIENTIFIC NAME<br>WARFARIN | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA Approval** | Yes |
| **US FDA** | Yes; 1954 |
| **EMA** | Yes |
| **MHRA** | Yes |
| **PMDA** | No |
| **Indication (ICD-10)** | I81 |
| **Drug Class** | Antithrombotic agents |
| **Drug Sub-class** | Vitamin K antagonists |
| **ATC Code** | **B01AA03** |
| **DRUG INFORMATION** | |
| **Dosage Form** | Tablet |
| **Route of Administration** | Oral use |
| **Dose (Adult) [DDD]*** | **Starting dose 5 mg once daily** |
| **Maximum Daily Dose Adults*** | N/A |
| **Adjustment** | Renal impairment prior to treatment:<br>- No initial dosage adjustment necessary<br>Hepatic impairment prior to treatment: |

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| | - No dose adjustment required |
| **Prescribing edits*** | N/A |
| **AGE (Age Edit):** N/A | |
| **CU (Concurrent Use Edit):** N/A | |
| **G (Gender Edit):** N/A | |
| **MD (Physician Specialty Edit):** N/A | |
| **PA (Prior Authorization):** N/A | |
| **QL (Quantity Limit):** N/A | |
| **ST (Step Therapy):** N/A | |
| **EU (Emergency Use Only):** N/A | |
| **PE (Protocol Edit):** N/A | |
| **SAFETY** | |
| **Main Adverse Drug Reactions (most common and most serious)** | - Most common: bleeding; Bruise<br>- Most serious: Atheroemboli/cholesterol microemboli; Calciphylaxis; Decreased bone mineral density; Hemorrhage; Skin necrosis/gangrene |
| **Drug Interactions*** | Anticoagulants: May enhance the anticoagulant effect of Vitamin K Antagonists (Risk C)<br><br>**Category X:** defibrotide, hemin. |
| **Special Population** | Older adult<br>Patients with genomic variants in CYP2C9 and/or VKORC1 |
| **Pregnancy** | Use is contraindicated during pregnancy except in patients with mechanical heart valves who are at high risk for thromboembolism; use is also contraindicated in patients with threatened abortion, eclampsia, or preeclampsia. |
| **Lactation** | Warfarin is considered compatible with breastfeeding |
| **Contraindications** | - Hypersensitivity |

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| | - hemorrhagic tendencies<br>- recent or potential surgery of the eye or CNS<br>- major regional lumbar block anesthesia or traumatic surgery resulting in large<br>- malignant hypertension<br>- pericarditis or pericardial effusion<br>- bacterial endocarditis<br>- unsupervised patients with conditions associated with a high potential for noncompliance<br>- eclampsia/preeclampsia<br>- threatened abortion<br>- pregnancy |
| **Monitoring Requirements** | - Prothrombin time, INR; hematocrit; may consider genotyping of CYP2C9 and VKORC1 prior to initiation of therapy |
| **Precautions** | - Bleeding risk |
| **Black Box Warning** | Bleeding risk: Warfarin can cause major or fatal bleeding |
| **REMS*** | N/A |

**HEALTH TECHNOLOGY ASSESSMENT (HTA)**

HTA reviews and recommendations of PVT treatment with warfarin are not available by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC).

**CONCLUSION STATEMENT- Warfarin**

Warfarin is a Vitamin K antagonist. It is used for PVT treatment after achievement of rapid anticoagulation with LMWH. Once the patient is stable and no invasive procedures are planned, they may be switched to warfarin, and the INR should be between 2 and 3. In case of cirrhosis, non-warfarin-based therapy is preferable because the INR may not reflect the patient's level of anticoagulation. Limitations for the use of Warfarin include the risk of hypersensitivity, hemorrhagic tendencies,

recent or potential surgery of the eye or CNS. Warfarin should be avoided during pregnancy.

## 2.4 Fondaparinux

Information on Fondaparinux is detailed in the table below.

**Table 11.** Fondaparinux Drug Information

| SCIENTIFIC NAME<br>FONDAPARINUX | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA Approval** | Yes |
| **US FDA** | Yes; July 2001 |
| **EMA** | Yes; March 2002 |
| **MHRA** | Yes |
| **PMDA** | No |
| **Indication (ICD-10)** | I81 |
| **Drug Class** | Antithrombotic agents |
| **Drug Sub-class** | Factor Xa inhibitor |
| **ATC Code** | **B01AX05** |
| **DRUG INFORMATION** | |
| **Dosage Form** | Solution for injection |
| **Route of Administration** | Subcutaneous use |
| **Dose (Adult) [DDD]*** | 50 kg: 5 mg once daily.<br>50 to 100 kg: 7.5 mg once daily.<br>>100 kg: 10 mg once daily. |
| **Maximum Daily Dose Adults*** | 7.5 mg |
| **Adjustment** | Renal impairment prior to treatment:<br>- CrCl 50 to 80 mL/minute: No dosage adjustment necessary. However, total clearance reduced ~25% in patients with CrCl 50 to 80 mL/minute.<br>- CrCl 30 to 50 mL/minute: No dosage adjustment necessary. However, use with caution and monitor closely for bleeding as |

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| | accumulation can occur (Ref); total clearance reduced ~40% compared to patients with CrCl >80 mL/minute.<br>- CrCl < 30 mL/minute: Use is contraindicated. Total clearance is reduced ~55% compared to patients with CrCl >80 mL/minute.<br><u>Hepatic impairment prior to treatment</u>:<br>- Mild-to-moderate impairment (Child-Pugh class A and B): No dosage adjustment necessary; monitor for signs of bleeding.<br>- Severe impairment (Child-Pugh class C): There are no dosage adjustment provided in the manufacturer's labeling (has not been studied). Use with caution; monitor closely for signs of bleeding. |
| **Prescribing edits*** | MD |
| **AGE (Age Edit):** N/A | |
| **CU (Concurrent Use Edit):** N/A | |
| **G (Gender Edit): N/A** | |
| **MD (Physician Specialty Edit):** Only physicians specialized in hematology; cardiology; pneumology should prescribe Fondaparinux. | |
| **PA (Prior Authorization):** N/A | |
| **QL (Quantity Limit):** N/A | |
| **ST (Step Therapy):** N/A | |
| **EU (Emergency Use Only):** N/A | |
| **PE (Protocol Edit):** N/A | |
| **SAFETY** | |
| **Main Adverse Drug Reactions (most common and most serious)** | - Most common: Pain, bruising, redness, and swelling at the injection site<br>- Most serious: Anemia; hypotension |

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| **Drug Interactions*** | Vitamin K Antagonists (e.g., warfarin): Anticoagulants may enhance the anticoagulant effect of Vitamin K Antagonists (Risk C) |
| **Special Population** | Older adult<br>Patients <50 kg: |
| **Pregnancy** | Use of fondaparinux in pregnancy should be limited to those women who have severe allergic reactions to heparin, including HIT, and who cannot receive danaparoid |
| **Lactation** | The use of alternative anticoagulants is preferred |
| **Contraindications** | - Serious Hypersensitivity<br>- Severe renal impairment<br>- Body weight <50 kg<br>- active major bleeding<br>- bacterial endocarditis<br>- thrombocytopenia associated with a positive in vitro test for antiplatelet antibody in the presence of fondaparinux |
| **Monitoring Requirements** | - Periodically monitor CBC, platelet count, serum creatinine, occult blood testing of stools, signs and symptoms of bleeding. |
| **Precautions** | - Bleeding risk<br>- Thrombocytopenia |
| **Black Box Warning** | Epidural or spinal hematomas may occur in patients who are anticoagulated with low molecular weight heparins, heparinoids, or fondaparinux and are receiving neuraxial anesthesia or undergoing spinal puncture. |
| **REMS*** | N/A |

## HEALTH TECHNOLOGY ASSESSMENT (HTA)

HTA reviews and recommendations of PVT treatment with fondaparinux are not available by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC).

The table below lists the HTA reviews and recommendations of pulmonary embolism treatment with fondaparinux by these agencies/institutes/authorities.

**Table 12.** Fondaparinux HTA Analysis

| MEDICATION | AGENCY | DATE – HTA RECOMMENDATION |
|---|---|---|
| **Fondaparinux** | NICE | N/A |
| | CADTH | N/A |
| | HAS[58] | Opinion in favor of hospital management in the Marketing Authorization indications except for prolonged thromboprophylaxis after scheduled orthopedic knee or hip surgery |
| | IQWIG | N/A |
| | PBAC | N/A |

## CONCLUSION STATEMENT- Fondaparinux

Fondaparinux is a Factor Xa inhibitor, which can be used for PVT treatment. It is recommended at a dose not exceeding 7.5 mg. The HAS HTA declared its opinion in favor of hospital management in the Marketing Authorization indications except for prolonged thromboprophylaxis after scheduled orthopedic knee or hip surgery (HAS). Limitations for the use of Fondaparinux include serious hypersensitivity, severe renal impairment, body weight <50 kg, active major bleeding, and bacterial endocarditis.

## 2.5 Direct Oral Anticoagulants (DOACs)

### 2.5.1 Dabigatran

Information on Dabigatran is detailed in the table below.

**Table 13.** Dabigatran Drug Information

| SCIENTIFIC NAME<br>DABIGATRAN ETEXILATE | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA Approval** | Yes |
| **US FDA** | Yes; October 2010 |
| **EMA** | Yes; March 2008 |
| **MHRA** | Yes, data not available |
| **PMDA** | Yes; January 2011 |
| **Indication (ICD-10)** | I81 |
| **Drug Class** | Antithrombotic agents |
| **Drug Sub-class** | Direct factor Xa inhibitors |
| **ATC Code** | **B01AE07** |
| **DRUG INFORMATION** | |
| **Dosage Form** | Capsule, hard |
| **Route of Administration** | Oral use |
| **Dose (Adult) [DDD]*** | **150 mg twice daily** |
| **Maximum Daily Dose Adults*** | 300 mg |
| **Adjustment** | Renal impairment prior to treatment:<br>- eGFR ≥50 mL/minute/1.73 m2: No adjustment needed.<br>- eGFR <50 mL/minute/1.73 m2: Avoid use<br>Hepatic impairment prior to treatment:<br>- No dosage adjustments |
| **Prescribing edits*** | N/A |
| **AGE (Age Edit):** N/A | |
| **CU (Concurrent Use Edit):** N/A | |
| **G (Gender Edit):** N/A | |

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| **MD (Physician Specialty Edit):** N/A | |
| **PA (Prior Authorization):** N/A | |
| **QL (Quantity Limit):** N/A | |
| **ST (Step Therapy):** N/A | |
| **EU (Emergency Use Only):** N/A | |
| **PE (Protocol Edit):** N/A | |
| **SAFETY** | |
| **Main Adverse Drug Reactions (most common and most serious)** | - Most common: Gastrointestinal signs and symptoms<br>- Most serious: Hemorrhage |
| **Drug Interactions*** | Acalabrutinib; Agents with Antiplatelet Properties: May enhance the anticoagulant effect of Anticoagulants (risk C)<br><br>Aspirin: May enhance the adverse/toxic effect of Dabigatran Etexilate (Risk D)<br>Anticoagulants: Dabigatran Etexilate may enhance the anticoagulant effect of Anticoagulants (Risk X) |
| **Special Population** | Older adult: Use with extreme caution or consider other treatment options |
| **Pregnancy** | Use of direct-acting oral anticoagulants increases the risk of bleeding in all patients. When used in pregnancy, there is also the potential for fetal bleeding or subclinical placental bleeding which may increase the risk of miscarriage, preterm delivery, fetal compromise, or stillbirth |
| **Lactation** | Breastfeeding is not recommended by the manufacturer. Until safety data are available, direct-acting oral anticoagulants are not recommended for use in patients who are breastfeeding; use of an alternative anticoagulant is preferred |
| **Contraindications** | - Serious hypersensitivity |

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| | - Active pathological bleeding<br>- Patients with mechanical prosthetic heart valve(s) |
| **Monitoring Requirements** | - CBC, aPTT, PT, serum creatinine, and liver function tests prior to initiation, when clinically indicated, and at least annually<br>- Signs of bleeding |
| **Precautions** | - Bleeding risk<br>- Thromboembolic events<br>- Antiphospholipid syndrome<br>- GI/Bariatric surgery: Altered absorption<br>- Valvular heart disease: Use is not recommended in patients with valvular heart disease |
| **Black Box Warning** | Premature discontinuation increases the risk of thrombotic events<br>Increased risk of epidural or spinal hematoma when:<br>- Used with neuraxial anesthesia or spinal puncture<br>- With indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis<br>- By traumatic or repeated epidural or spinal puncture |
| **REMS*** | N/A |

**HEALTH TECHNOLOGY ASSESSMENT (HTA)**

HTA reviews and recommendations of portal vein thrombosis treatment options are not available by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC).

**CONCLUSION STATEMENT- Dabigatran**

The use of Dabigatran is regarded as a first line treatment for patients who had PVT unless contraindicated or unless side effects are developed. It is recommended at a dose not exceeding 300 mg/j. Limitations for the use of Dabigatran include the risk of severe hypersensitivity (i.e., anaphylactic reactions) and active pathological bleeding. Dabigatran should be avoided during pregnancy and for patients with CKD.

### 2.5.2 Edoxaban

Information on Edoxaban is detailed in the table below.

**Table 14.** Edoxaban Drug Information

| SCIENTIFIC NAME<br>EDOXABAN TOSILATE | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA Approval** | Yes |
| **US FDA** | Yes; January 2015 |
| **EMA** | Yes; June 2015 |
| **MHRA** | Yes, data not available |
| **PMDA** | Yes; April 2011 |
| **Indication (ICD-10)** | I81 |
| **Drug Class** | Antithrombotic agents |
| **Drug Sub-class** | Direct factor Xa inhibitors |
| **ATC Code** | **B01AF03** |
| **DRUG INFORMATION** | |
| **Dosage Form** | Film-coated tablet |
| **Route of Administration** | Oral use |
| **Dose (Adult) [DDD]*** | **Patient weight >60 kg: 60 mg once daily.**<br>**Patient weight ≤60 kg: 30 mg once daily** |
| **Maximum Daily Dose Adults*** | 60 mg |
| **Adjustment** | Renal impairment prior to treatment:<br>- CrCl >50 mL/minute:<br>- CrCl 15 to 50 mL/minute: Oral: 30 mg once daily. |

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| | - CrCl <15 mL/minute: Use is not recommended.<br><u>Hepatic impairment prior to treatment</u>:<br>- Mild impairment (Child-Pugh class A): No dosage adjustment necessary.<br>- Moderate to severe impairment (Child-Pugh class B and C): Use is not recommended. |
| **Prescribing edits*** | N/A |
| **AGE (Age Edit):** N/A | |
| **CU (Concurrent Use Edit):** N/A | |
| **G (Gender Edit):** N/A | |
| **MD (Physician Specialty Edit):** N/A | |
| **PA (Prior Authorization):** N/A | |
| **QL (Quantity Limit):** N/A | |
| **ST (Step Therapy):** N/A | |
| **EU (Emergency Use Only):** N/A | |
| **PE (Protocol Edit):** N/A | |
| **SAFETY** | |
| **Main Adverse Drug Reactions (most common and most serious)** | - Most common: minor hemorrhage<br>- Most serious: major hemorrhage |
| **Drug Interactions*** | Acalabrutinib; Agents with Antiplatelet Properties: May enhance the anticoagulant effect of Anticoagulants (risk C)<br><br>Aspirin: May enhance the adverse/toxic effect of edoxaban (Risk D)<br>Anticoagulants: edoxaban may enhance the anticoagulant effect of Anticoagulants (Risk X) |
| **Special Population** | N/A |
| **Pregnancy** | Use of direct-acting oral anticoagulants increases the risk of bleeding in all patients. When used in pregnancy, |

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| | there is also the potential for fetal bleeding or subclinical placental bleeding which may increase the risk of miscarriage, preterm delivery, fetal compromise, or stillbirth. Agents other than edoxaban are preferred for the treatment of AF or VTE in pregnant patients |
| **Lactation** | Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer. Until safety data are available, direct-acting oral anticoagulants are not recommended for use in patients who are breastfeeding; use of an alternative anticoagulant is preferred |
| **Contraindications** | - Active pathological bleeding |
| **Monitoring Requirements** | - CBC, aPTT, PT, serum creatinine, and liver function tests prior to initiation, when clinically indicated, and at least annually |
| **Precautions** | - Bleeding risk<br>- Thromboembolic events<br>- Antiphospholipid syndrome<br>- GI/Bariatric surgery: Altered absorption<br>- Valvular heart disease: Use is not recommended in patients with valvular heart disease<br>- Nonvalvular atrial fibrillation: Do not administer to nonvalvular atrial fibrillation (NVAF) patients with CrCl >95 mL/minute |
| **Black Box Warning** | Premature discontinuation increases the risk of thrombotic events<br>Increased risk of epidural or spinal hematoma when:<br>- Used with neuraxial anesthesia or spinal puncture |

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| | - With indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis<br>- By traumatic or repeated epidural or spinal puncture<br>Reduced efficacy in nonvalvular atrial fibrillation patients with CrCl >95 mL/minute: increased rate of ischemic stroke |
| **REMS*** | N/A |

## HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Portal vein thrombosis treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. The recommendations below are for Edoxaban.

**Table 15.** Edoxaban HTA Analysis

| MEDICATION | AGENCY | DATE – HTA RECOMMENDATION |
|---|---|---|
| **Edoxaban** | NICE | N/A |
| | CADTH | May 25, 2017, the CADTH Canadian Drug Expert Committee (CDEC) recommends that edoxaban be reimbursed for the treatment of venous thromboembolism (VTE) (deep vein thrombosis [DVT], pulmonary embolism [PE]) and the prevention of recurrent DVT and PE, if the following condition is met:<br>Condition:<br>• Substantial reduction in price |
| | HAS | N/A |
| | IQWIG | N/A |
| | PBAC | N/A |

**CONCLUSION STATEMENT- Edoxaban**

**The use of Edoxaban is regarded as a first line treatment of PVT**. It is recommended at a dose not exceeding 60 mg/j. Its use is backed up by several HTA bodies namely CADTH. Limitations for the use of edoxaban include the risk of severe hypersensitivity (ie, anaphylactic reactions) and active pathological bleeding. Edoxaban should be avoided during pregnancy.

### 2.5.3 Apixaban

Information on Apixaban is detailed in the table below.

**Table 16.** Apixaban Drug Information

| SCIENTIFIC NAME<br>APIXABAN | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA Approval** | Yes |
| **US FDA** | Yes, 2014 |
| **EMA** | Yes, May 2011 |
| **MHRA** | Yes, data not available |
| **PMDA** | Yes; December 2012 |
| **Indication (ICD-10)** | I81 |
| **Drug Class** | Antithrombotic agents |
| **Drug Sub-class** | Direct factor Xa inhibitors |
| **ATC Code** | **B01AF02** |
| **DRUG INFORMATION** | |
| **Dosage Form** | Film-coated tablet |
| **Route of Administration** | Oral use |
| **Dose (Adult) [DDD]*** | **10 mg twice daily for 7 days followed by 5 mg twice daily** |
| **Maximum Daily Dose Adults*** | 20 mg |

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| **Adjustment** | Renal impairment prior to treatment:<br>No dosage adjustment is recommended by the manufacturer for any degree of reduced kidney function.<br>Hepatic impairment prior to treatment:<br>- Mild impairment (Child-Pugh class A): No dosage adjustment required.<br>- Moderate impairment (Child-Pugh class B): There are no dosage adjustments provided in manufacturer's labeling; use with caution (limited clinical experience in these patients).<br>Severe impairment (Child-Pugh class C): Use is not recommended. |
| **Prescribing edits*** | N/A |
| **AGE (Age Edit):** N/A | |
| **CU (Concurrent Use Edit):** N/A | |
| **G (Gender Edit):** N/A | |
| **MD (Physician Specialty Edit):** N/A | |
| **PA (Prior Authorization):** N/A | |
| **QL (Quantity Limit):** N/A | |
| **ST (Step Therapy):** N/A | |
| **EU (Emergency Use Only):** N/A | |
| **PE (Protocol Edit):** N/A | |
| **SAFETY** | |
| **Main Adverse Drug Reactions (most common and most serious)** | - Most common: Hypersensitivity; hemorrhage<br>- Most serious: major bleeding; spinal or epidural hematomas |
| **Drug Interactions*** | Urokinase; St John's Wort; Mifepristone; Edoxaban; Defibrotide; Dabigatran: Risk X |
| **Special Population** | Acutely ill medical patients<br>Older adult |
| **Pregnancy** | Information specific to the use of |

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| | apixaban in pregnancy is limited. Use of direct acting oral anticoagulants increases the risk of bleeding in all patients.<br>When used in pregnancy, there is also the potential for fetal bleeding or subclinical placental bleeding which may increase the risk of miscarriage, preterm delivery, fetal compromise, or stillbirth |
| **Lactation** | Direct acting oral anticoagulants are not recommended for use in patients who are breastfeeding; use of an alternative anticoagulant is preferred |
| **Contraindications** | Severe hypersensitivity (ie, anaphylactic reactions); Active pathological bleeding |
| **Monitoring Requirements** | - CBC, aPTT, PT, serum creatinine, and liver function tests prior to initiation and at least annually<br>- INR testing: When converting from apixaban to a vitamin K antagonist (VKA)<br>- Signs and symptoms of neurologic impairment: if receiving apixaban therapy during neuraxial anesthesia |
| **Precautions** | - In hemodynamically unstable patients with acute PE or patients with PE requiring thrombolysis or pulmonary embolectomy, the use of apixaban is not recommended as an alternative to unfractionated heparin for initial treatment.<br>- Spinal or epidural hematoma<br>- Bleeding risk<br>- not recommended for patients with triple-positive antiphospholipid syndrome |
| **Black Box Warning** | Premature discontinuation apixaban, increases risk of thrombotic events |

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| | Increased risk of epidural or spinal hematoma when:<br>- Used with neuraxial anesthesia or spinal puncture<br>- With indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis<br>- By traumatic or repeated epidural or spinal puncture |
| **REMS*** | N/A |

**HEALTH TECHNOLOGY ASSESSMENT (HTA)**

HTA reviews and recommendations of portal vein thrombosis treatment options are not available by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC).

**CONCLUSION STATEMENT- Apixaban**

The use of Apixaban is regarded as a first line treatment of PVT unless contraindicated or unless side effects are developed. It is recommended at a dose not exceeding 20mg/j. Limitations for the use of apixaban include the risk of severe hypersensitivity (i.e., anaphylactic reactions) and active pathological bleeding. Apixaban should be avoided during pregnancy.

### 2.5.4 Rivaroxaban

Information on Rivaroxaban is detailed in the table below.

**Table 17.** Rivaroxaban Drug Information

| SCIENTIFIC NAME<br>RIVAROXABAN | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA Approval** | Yes |
| **US FDA** | Yes; July 2011 |
| **EMA** | Yes; September 2008 |
| **MHRA** | Yes, data not available |

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|---|---|
| **PMDA** | Yes; January 2021 |
| **Indication (ICD-10)** | I81 |
| **Drug Class** | Antithrombotic agents |
| **Drug Sub-class** | Direct factor Xa inhibitors |
| **ATC Code** | **B01AF01** |
| **DRUG INFORMATION** | |
| **Dosage Form** | Film-coated tablet |
| **Route of Administration** | Oral use |
| **Dose (Adult) [DDD]*** | **15 mg twice daily with food for 21 days followed by 20 mg once daily with food** |
| **Maximum Daily Dose Adults*** | 30 mg |
| **Adjustment** | Renal impairment prior to treatment:<br>- CrCl ≥30 mL/minute: No dosage adjustment necessary.<br>- CrCl 15 to <30 mL/minute: Avoid use<br>Hepatic impairment prior to treatment:<br>- Mild impairment (Child-Pugh class A): No dosage adjustment required.<br>- Moderate impairment (Child-Pugh class B): se of other direct oral anticoagulant agents with a more favorable pharmacokinetic profile in hepatic impairment are generally preferred (eg, apixaban, dabigatran)<br>- Severe impairment (Child-Pugh class C): Use is not recommended. |
| **Prescribing edits*** | N/A |
| **AGE (Age Edit):** N/A | |
| **CU (Concurrent Use Edit):** N/A | |
| **G (Gender Edit):** N/A | |
| **MD (Physician Specialty Edit):** N/A | |
| **PA (Prior Authorization):** N/A | |
| **QL (Quantity Limit):** N/A | |
| **ST (Step Therapy):** N/A | |

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|---|---|
| **EU (Emergency Use Only):** N/A | |
| **PE (Protocol Edit):** N/A | |
| **SAFETY** | |
| **Main Adverse Drug Reactions (most common and most serious)** | - Most common: Hypersensitivity; hemorrhage, Heavy menstrual bleeding<br>- Most serious: major bleeding; major hemorrhage, Spinal or epidural hematomas |
| **Drug Interactions*** | Urokinase; Edoxaban; Defibrotide; Dabigatran: May enhance the anticoagulant effect of Rivaroxaban (risk X) |
| **Special Population** | Older adult: Use with caution |
| **Pregnancy** | Use of direct acting oral anticoagulants increases the risk of bleeding in all patients. When used in pregnancy, there is also the potential for fetal bleeding or subclinical placental bleeding which may increase the risk of miscarriage, preterm delivery, fetal compromise, or stillbirth |
| **Lactation** | Until safety data are available, direct acting oral anticoagulants are not recommended for use in patients who are breastfeeding; use of an alternative anticoagulant is preferred |
| **Contraindications** | - Severe hypersensitivity<br>- Hepatic disease (including Child-Pugh classes B and C) associated with coagulopathy and clinically relevant bleeding risk |
| **Monitoring Requirements** | - Kidney function and CBC prior to initiation and at least annually for all patients<br>- hepatic function<br>- signs and symptoms of bleeding<br>- unexplained decrease in hemoglobin |

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| **Precautions** | - Spinal or epidural hematoma<br>- Bleeding risk<br>- not recommended for patients with triple-positive antiphospholipid syndrome<br>- Hepatic impairment<br>- Kidney impairment<br>- Avoid use in patients with surgically implanted mechanical heart valve |
| **Black Box Warning** | Premature discontinuation apixaban, increases risk of thrombotic events<br><br>Increased risk of epidural or spinal hematoma when:<br>- Used with neuraxial anesthesia or spinal puncture<br>- With indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis<br>- By traumatic or repeated epidural or spinal puncture |
| **REMS*** | N/A |

## HEALTH TECHNOLOGY ASSESSMENT (HTA)

HTA reviews and recommendations of portal vein thrombosis treatment options are not available by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC).

## CONCLUSION STATEMENT- Rivaroxaban

The use of Rivaroxaban is regarded as a first line treatment of PVT unless contraindicated or unless side effects are developed. It is recommended at a dose not exceeding 30mg/j. Limitations for the use of Rivaroxaban include the risk of severe hypersensitivity (ie, anaphylactic reactions) and active pathological bleeding. Rivaroxaban should be avoided during pregnancy.

### 2.6 Other Therapeutic Options

This section includes drugs that are used for the management of PVT but are not currently registered by the SFDA.

#### 2.6.1 Streptokinase

Streptokinase was approved by the FDA in October 1996. It is a thrombolytic agent to dissolve blood clots. It is used in the treatment of PVT.

## Section 3.0 Key Recommendations Synthesis

**Acute PVT:**

In the absence of excessive bleeding risk (large esophageal varices), anticoagulation is recommended for the treatment of PVT rather than expectant management, especially in the acute setting. Predisposing conditions should always be managed as well in parallel. The first therapeutic line is a LMWH to achieve rapid anticoagulation. Then, switching to an oral anticoagulant is advised once the patient's condition has stabilized and no invasive procedures are planned. If warfarin is chosen, INR goal is 2 to 3. In cirrhotic patients, non-warfarin-based therapy is preferable since the INR may not reflect the patient's level of anticoagulation.

When there is a transient or correctable thrombotic risk factors (e.g. pancreatitis) or when no thrombotic risk factor is identified, it is suggested to treat with anticoagulation for six months rather than long-term. For patients with permanent thrombotic risk factors that cannot be corrected, long-term anticoagulation rather than six months anticoagulation is suggested. Additionally, long-term therapy may also be indicated for patients with acute PVT that extends into the mesenteric veins, given the risk of intestinal infarction in such patients.

**Chronic PVT:**

Anticoagulation may be indicated for some patients with chronic PVT: the goal is to prevent recurrent thrombosis and thrombus extension, to maintain splanchnic venous drainage, to relieve symptoms, and to promote recanalization in patients with cirrhosis. However, the risk of recurrent thrombosis must be weighed against the risk for bleeding. The decision to start anticoagulation must be made on a case-by-case basis, using the following criteria:

- Patient's risk of bleeding (e.g. large varices with features associated with an increased risk of bleeding)
- Patient's risk of a thrombotic event (e.g. underlying prothrombotic disorder)
- Patient’s chances to survive a bleed or a thrombotic event

- Liver transplantation waiting list
- Presence of symptoms (e.g. abdominal pain)
- Anticoagulation is indicated for patients who are at increased risk for recurrent thrombosis based on their clinical history or laboratory studies, or those who are awaiting LT, provided their bleeding or death risk is not increased. Patients at increased risk for thrombosis are those with inherited prothrombotic disorders, decompensated cirrhosis, or malignancy.

Patients who are at increased risk for bleeding, unlikely to survive a bleeding episode, or not at increased risk for recurrent thrombosis, expectant management is suggested rather than anticoagulation. Patients at increased risk of bleeding are those with large varices who have not had adequate prophylactic measures to prevent bleeding. Patients not at increased risk for thrombosis are those with PVT that developed due to a transient event, such as transient hypovolemia, and who do not have any underlying disorders predisposing to thrombosis.

## Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of portal vein thrombosis. These recommendations should be used to support and not supplant decisions in individual patient management.

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# Section 6.0 Appendices

## Appendix A. Prescribing Edits Definition

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

| Prescribing edits Tools | Description |
|---|---|
| **AGE (Age):** | Coverage may depend on patient age |
| **CU (Concurrent Use):** | Coverage may depend upon concurrent use of another drug |
| **G (Gender):** | Coverage may depend on patient gender |
| **MD (Physician Specialty):** | Coverage may depend on prescribing physician's specialty or board certification |
| **PA (Prior Authorization):** | Requires specific physician request process |
| **QL (Quantity Limits):** | Coverage may be limited to specific quantities per prescription and/or time period |
| **ST (Step Therapy):** | Coverage may depend on previous use of another drug |
| **EU (Emergency Use only):** | This drug status on Formulary is only for emergency use |
| **PE (Protocol Edit):** | Use of drug is dependent on protocol combination, doses and sequence of therapy |

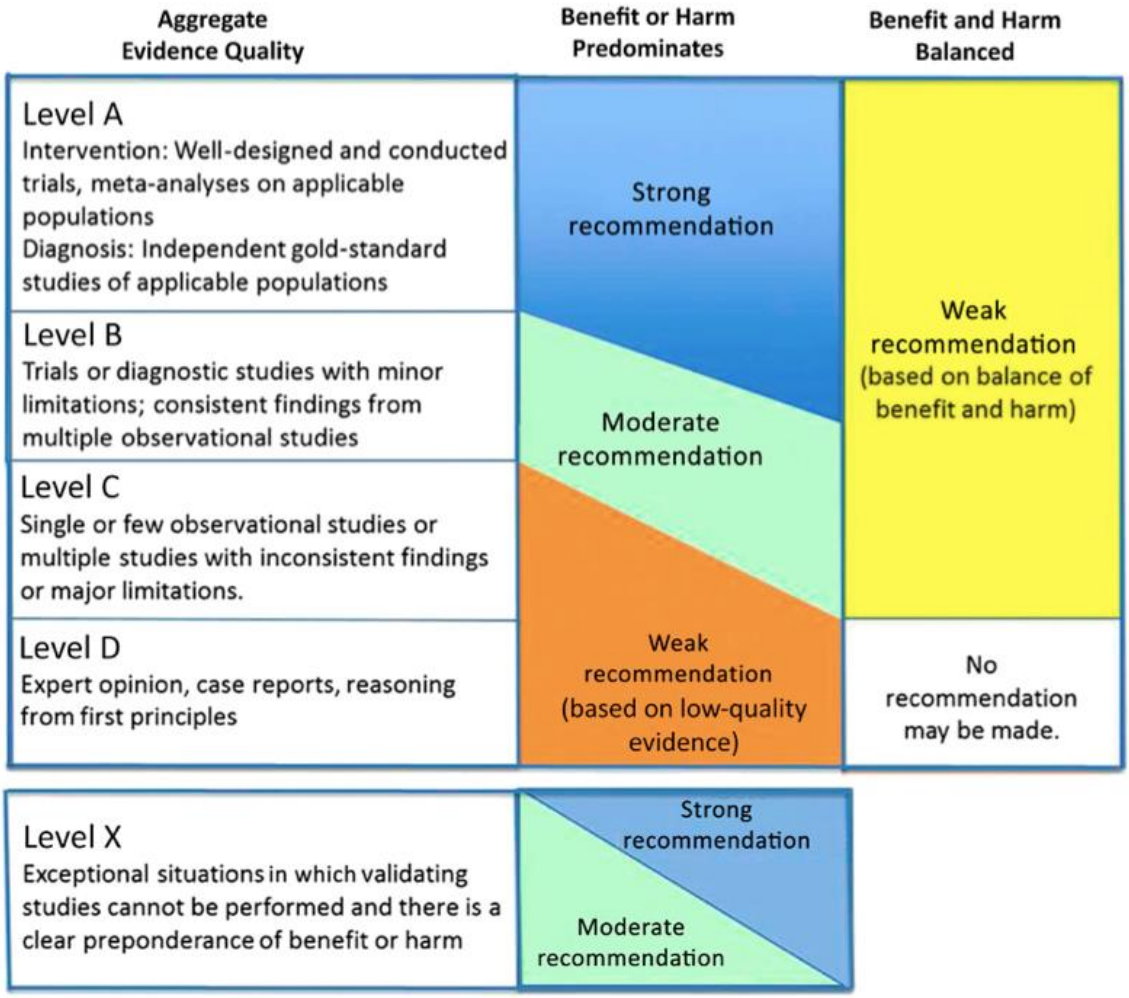
## Appendix B. PubMed Search Methodology Terms

The following PubMed Search Methodology was opted:

| Query | Filters | Search Details | Results |
|---|---|---|---|
| ((((((((((((((((((((((((Venous Thrombosis[MeSH Terms]) OR (Phlebothrombosis[Title/Abstract])) OR (Phlebothromboses[Title/Abstract])) OR (Thrombosis, Venous[Title/Abstract])) OR (Thromboses, Venous[Title/Abstract])) OR (Venous Thromboses[Title/Abstract])) OR (Deep Vein Thrombosis[Title/Abstract])) OR (Deep Vein Thromboses[Title/Abstract])) OR (Thromboses, Deep Vein[Title/Abstract])) OR (Vein Thromboses, Deep[Title/Abstract])) OR (Vein Thrombosis, Deep[Title/Abstract])) OR (Deep-Venous Thrombosis[Title/Abstract])) OR (Deep-Venous Thromboses[Title/Abstract])) OR (Thromboses, Deep-Venous[Title/Abstract])) OR (Thrombosis, Deep-Venous[Title/Abstract])) OR (Deep-Vein Thrombosis[Title/Abstract])) OR (Deep-Vein Thromboses[Title/Abstract])) OR (Thromboses, Deep-Vein[Title/Abstract])) OR (Thrombosis, Deep-Vein[Title/Abstract])) OR (Thrombosis, Deep Vein[Title/Abstract])) OR (Deep Venous Thrombosis[Title/Abstract])) OR (Deep Venous | Meta-Analysis, in the last 5 years | (("venous thrombosis"[MeSH Terms] OR "Phlebothrombosis"[Title/Abstract] OR "Phlebothromboses"[Title/Abstract] OR "thrombosis venous"[Title/Abstract] OR "thromboses venous"[Title/Abstract] OR "venous thromboses"[Title/Abstract] OR "deep vein thrombosis"[Title/Abstract] OR "deep vein thromboses"[Title/Abstract] OR (("thrombose"[All Fields] OR "thrombosing"[All Fields] OR "Thrombosis"[MeSH Terms] OR "Thrombosis"[All Fields] OR "thrombosed"[All Fields] OR "Thromboses"[All Fields]) AND "Deep-Vein"[Title/Abstract]) OR (("veins"[MeSH Terms] OR "veins"[All Fields] OR "Vein"[All Fields]) AND "thromboses deep"[Title/Abstract]) OR "vein thrombosis deep"[Title/Abstract] OR "deep venous thrombosis"[Title/Abstract] OR "deep venous thromboses"[Title/Abstract] OR "thromboses deep venous"[Title/Abstract] OR "thrombosis deep venous"[Title/Abstract] OR "deep vein thrombosis"[Title/Abstract] OR "deep vein thromboses"[Title/Abstract] OR | 0 |

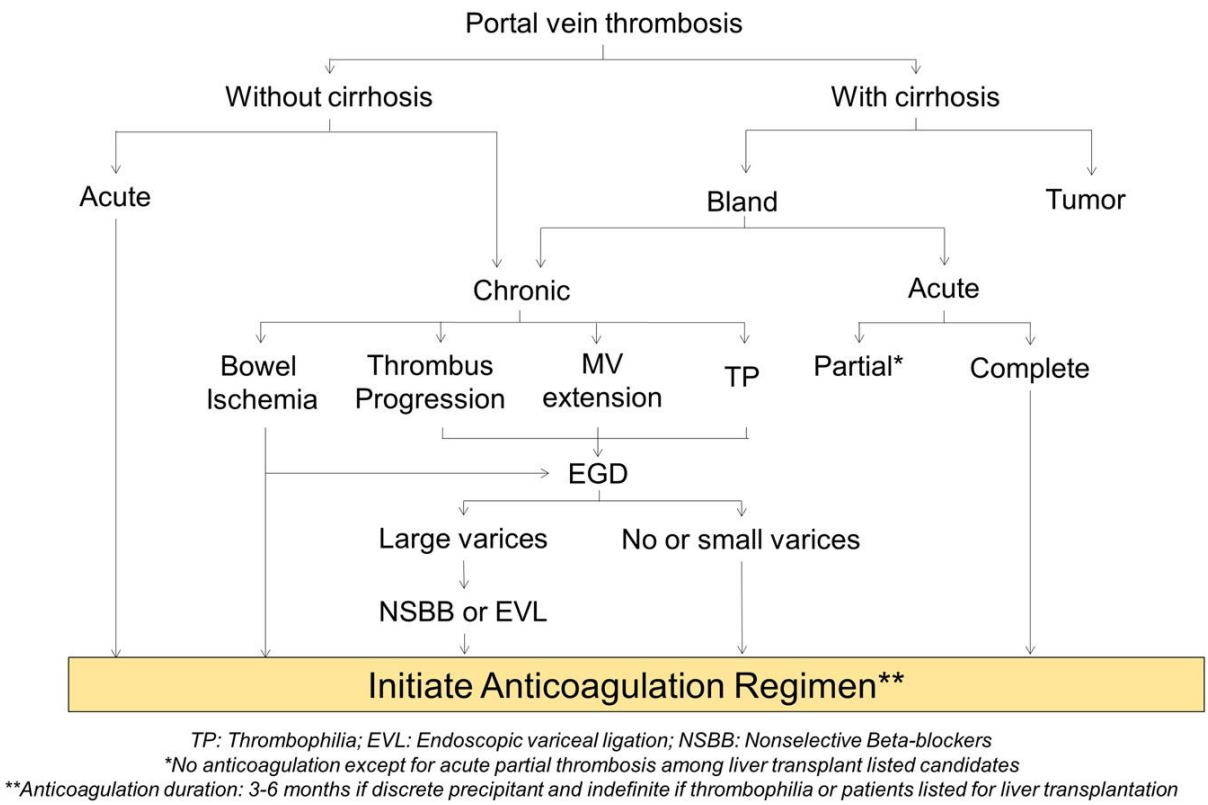
| | | | |
|---|---|---|---|
| Thromboses[Title/Abstract])) OR (Thromboses, Deep Venous[Title/Abstract])) OR (Thrombosis, Deep Venous[Title/Abstract])) OR (Venous Thromboses, Deep[Title/Abstract])) OR (Venous Thromboses, Deep[Title/Abstract])) AND (Venous Thrombosis, Deep[Title/Abstract]) | | (("thrombose"[All Fields] OR "thrombosing"[All Fields] OR "Thrombosis"[MeSH Terms] OR "Thrombosis"[All Fields] OR "thrombosed"[All Fields] OR "Thromboses"[All Fields]) AND "Deep-Vein"[Title/Abstract]) OR "thrombosis deep vein"[Title/Abstract] OR "thrombosis deep vein"[Title/Abstract] OR "deep venous thrombosis"[Title/Abstract] OR "deep venous thromboses"[Title/Abstract] OR "thromboses deep venous"[Title/Abstract] OR "thrombosis deep venous"[Title/Abstract] OR "venous thromboses deep"[Title/Abstract] OR "venous thromboses deep"[Title/Abstract]) AND "venous thrombosis deep"[Title/Abstract]) AND ((y_5[Filter]) AND (meta-analysis[Filter])) | |

## Appendix C. Level of Evidence




| Statement | Definition | Implication |
|---|---|---|
| Strong recommendation | A particular action is favored because anticipated benefits clearly exceed harms (or vice versa), and quality of evidence is excellent or unobtainable. | Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present. |
| Moderate recommendation | A particular action is favored because anticipated benefits clearly exceed harms (or vice versa), and the quality of evidence is good but not excellent (or is unobtainable). | Clinicians would be prudent to follow a moderate recommendation but should remain alert to new information and sensitive to patient preferences. |
| Weak recommendation (based on low-quality evidence) | A particular action is favored because anticipated benefits clearly exceed harms (or vice versa), but the quality of evidence is weak. | Clinicians would be prudent to follow a weak recommendation but should remain alert to new information and sensitive to patient preferences. |
| Weak recommendation (based on balance of benefits and harms) | A weak recommendation is provided when the aggregate database shows evidence of both benefit and harm that appears to be similar in magnitude for any available courses of action. | Clinicians should consider the options in their decision-making, but patient preference may have a substantial role. |

## Appendix D. Treatment Algorithm




*TP: Thrombophilia; EVL: Endoscopic variceal ligation; NSBB: Nonselective Beta-blockers*
**No anticoagulation except for acute partial thrombosis among liver transplant listed candidates*
***Anticoagulation duration: 3-6 months if discrete precipitant and indefinite if thrombophilia or patients listed for liver transplantation*

***Figure 3.*** *Treatment algorithm for the management of portal vein thrombosis (retrieved from the ACG 2020 guidelines)*