9 Transjugular Intrahepatic Portosystemic Shunt for Non-malignant Portal Vein Thrombosis

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Abstract

Portal vein thrombosis (PVT) is characterised by the presence of thrombus in the main portal vein, with or without intra-hepatic or mesenteric extension. PVT can arise in a non-cirrhotic liver, or on a background of cirrhosis. The etiologies, natural history, prognosis and therapeutic implications differ in both groups accordingly. Currently, anticoagulation is primarily recommended for those with acute PVT but is fraught with a theoretical risk of bleeding. Surgical therapy in these patients might be over-aggressive. In the past, transjugular intrahepatic portosystemic shunt (TIPS) placement was considered a relative contraindication in patients with PVT but now has been shown to be safe and efficacious in these patients, both with and without cirrhosis, with some caveats and modifications. What remains to be explored is the stage at which TIPS should be offered and whether it should be preferred over therapeutic anticoagulation. Randomized controlled trials are needed to answer this question.

Keywords

Cirrhosis · EHPVO · Anticoagulation · Intervention · TIPS · NCPF · HCC · liver Vascular · DOAC · Dabigatran · LT

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9.1 Introduction

Portal vein thrombosis (PVT), as the term suggests, is characterized by thrombosis in the main portal vein trunk, with or without extension into intra-hepatic portal vein branches and/or mesenteric vessels. It may occur on a background of cirrhosis, or without any evidence of chronic liver disease. Both these sub-groups differ from each other in terms of etiology, natural history and therapeutic options [1]. An important feature of PVT, which has prognostic and therapeutic implications, is the acute or chronic nature of thrombosis at the time of presentation. A stable patient of cirrhosis with new-onset PVT may present with acute decompensation (worsening of jaundice and ascites). In a patient with hepatocellular carcinoma (HCC), acute PVT may lead to acute worsening of liver function. Thus, PVT may lead to a change in the natural history of cirrhosis/liver disease.

Anticoagulation plays an important role in the management of PVT. Traditionally, transjugular intrahepatic portosystemic shunt (TIPS) has been thought to be relatively contraindicated in the setting of PVT [2]. However, over the last 2 decades, more experiences have been gained with TIPS in PVT cases, and it has been established as a valid therapeutic option [3]. A number of meta-analyses that have been published recently [4, 5] highlight the interest in the use of TIPS for PVT management.

9.2 Epidemiology

The epidemiologic data on non-cirrhotic PVT is sparse. A recent Italian study examining 3535 patients admitted in hospital over 10 years estimated the risk to be 3.8 per 100,000 inhabitants in males and 1.7 per 100,000 inhabitants in females [6]. A limitation of this study was that only symptomatic, hospitalized patients were included. The population prevalence of PVT based on autopsy series has been estimated to be around 1% [7]. The prevalence of PVT in compensated cirrhosis varies from 0.6% to 16%. In comparison, the prevalence in patients awaiting liver transplantation is around 10% (2–23%) [8]. In patients with HCC, the prevalence may be as high as 35% [9, 10]. The incidence may be affected by risk factors, which include age, gender, hypercoagulable states, study region, drugs and underlying chronic diseases. Various observational and clinical trials have also reported the incidence of PVT. Francoz et al. estimated PVT incidence to be 7% in patients waiting for liver transplantation (LT) when screened with Doppler ultrasonography [11].

9.3 Natural History and Prognosis

The natural history and prognosis of PVT differ among patients with and without cirrhosis. Another important factor that determines the outcome is the stage of presentation- acute or chronic. The data on the natural history of acute non-cirrhotic

PVT is sparse. The aim of early therapy in such a scenario is to prevent the progression of thrombus into the mesenteric vessels and promote recanalization of the portal vein, thereby preventing the development of intestinal ischemia and portal hypertension-related complications in the long term [12, 13]. Plessier et al. [13] in a prospective multicentre study included 102 patients with acute PVT without cirrhosis. Of these, 95 (93.1%) patients received anticoagulation. Over a median follow up of 234 days, anticoagulation therapy led to an increased rate of patency of the portal vein (left or right branch)- 39% vs. 13% at presentation, the splenic vein (SV)- 80% vs. 57% at presentation, and the superior mesenteric vein (SMV)- 73% vs. 42% at presentation. Progression to ischemia and infarction and death were reported in 2% of patients, each [13].

The natural history of chronic PVT in non-cirrhotic patients comes under the spectrum of extra-hepatic portal venous obstruction (EHPVO), which frequently presents as well tolerated acute variceal bleed and symptomatic moderate splenomegaly in the first decade of life, and a minority of patients may develop symptomatic portal cavernoma cholangiopathy, minimal hepatic encephalopathy (MHE), ascites, jaundice and terminal decompensation as a result of parenchymal extinction [14].

The natural history of PVT in cirrhosis is ominous and often heralds acute decompensation- worsening of jaundice, ascites, encephalopathy or detection of HCC [1]. PVT is diagnosed more frequently in patients with cirrhosis because of frequent imaging done for screening for HCC. The spontaneous recanalization rate of up to 40% has been reported [15]. The complexity of LT increases in patients with PVT, and the reported post-transplant outcomes are inferior as compared to cases without PVT [16].

9.4 Diagnostic Evaluation

Four important questions need to be answered on imaging before proceeding to the treatment of PVT. a) Is there any evidence of cirrhosis or not? b) Is the PVT acute or chronic? c) Is the thrombus bland or associated with a tumour? d) Is there an extension of thrombus into intrahepatic branches and mesenteric vessels?

Doppler ultrasonography is the first-line investigation. The thrombus appears as hypoechoic to isoechoic content within the lumen of the portal vein. Associated findings include the presence of collaterals and cavernoma. The presence of cavernoma usually indicates the chronic nature of PVT. However, cavernoma may develop within 6 days from the onset of acute PVT [17]. Doppler mode may also show the absence of flow within the portal vein. The presence of cirrhosis and other features of portal hypertension can also be inferred from the ultrasonography. Cross-sectional imaging with multiphase computed tomography is very helpful. It adds to the information given by Doppler ultrasound- the porto-mesenteric venous system can be visualized in its entirety, and the extension of thrombus into the mesenteric system with associated intestinal ischemia can also be inferred. The

presence of an enhancing, lumen-distending thrombus associated with an enhancing tumour in the cirrhotic liver, especially with high alpha-fetoprotein levels, is highly ominous for a malignant thrombus due to HCC [18].

9.5 TIPS as a Therapeutic Option for Non-malignant PVT

The role of TIPS in PVT patients with and without cirrhosis is discussed separately (Fig. 9.1). Senzolo et al. were one of the earliest to show in a large series that TIPS can be successfully placed in the setting of PVT. However, their study included a heterogeneous population of patients with cirrhosis and non-cirrhosis and those with or without cavernoma. Hence their findings cannot be generalized to all [3].

9.5.1 TIPS Technique

TIPS approach is affected by multiple factors, including the extent of PVT, the expertise of the interventional staff, and the presence of ascites. TIPS can be attempted with a transjugular approach alone (Fig. 9.2a), a combined transjugular

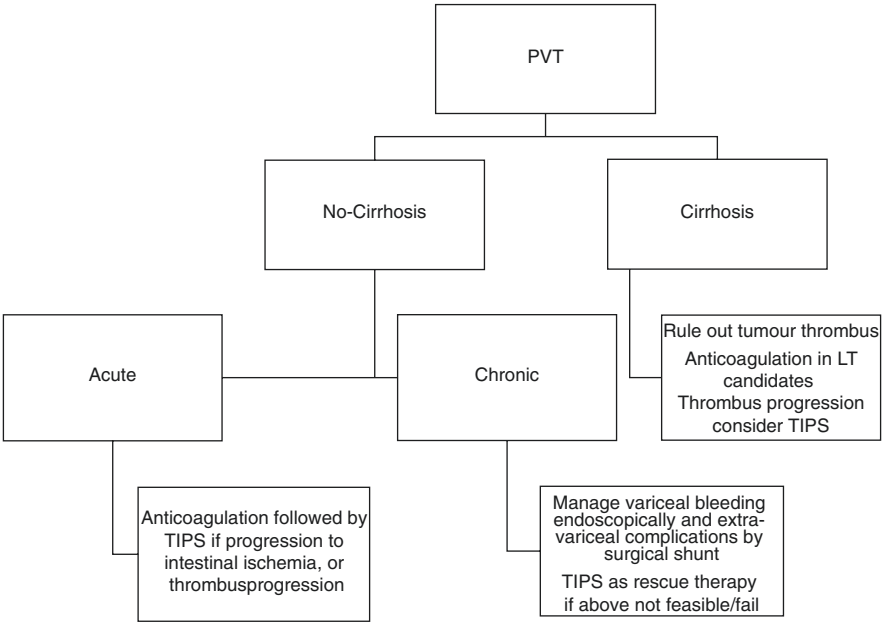

Fig. 9.1 Algorithm for management of PVT and the role of TIPS. *PVT* portal vein thrombosis, *TIPS* transjugular intrahepatic portosystemic shunt, *LT* liver transplantation

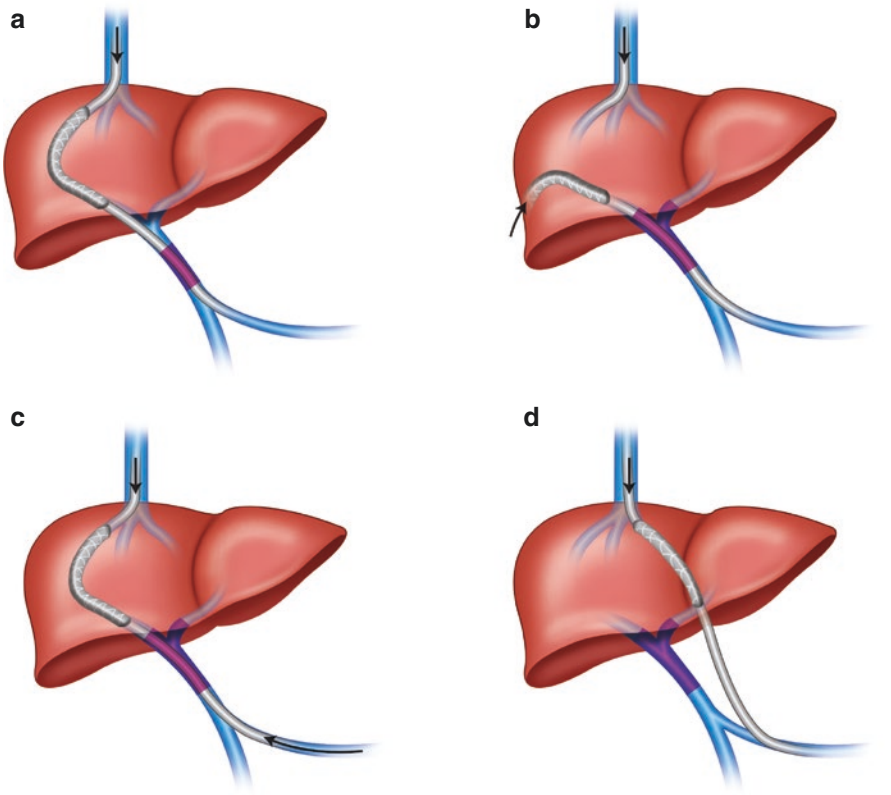

Fig. 9.2 TIPS approach in the setting of portal vein thrombosis (**a**) transjugular, (**b**) combined transhepatic and transjugular, (**c**) combined transsplenic and transjugular, (**d**) placement of TIPS through a large collateral in whom the main portal vein cannot be recanalized

and transhepatic approach (Fig. 9.2b), or a combined transjugular and transsplenic approach (Fig. 9.2c). TIPS can be placed into a recanalized main portal vein or else a dominant collateral vein (Fig. 9.2d). The use of combined transjugular and percutaneous transhepatic/transsplenic approach is recommended if intrahepatic portal vein branches are not visualized or cannot be cannulated via the transjugular approach alone. This combined approach carries a higher risk of bleeding since it involves capsular puncture; hence embolization of the percutaneous tract has been recommended [19].

9.5.2 TIPS for Acute Non-cirrhotic PVT

The standard treatment of acute non-cirrhotic PVT is anticoagulation for at least 6 months; prolonged therapy is recommended in patients with a prothrombotic state [20]. Despite adequate anticoagulation, complete recanalization occurs only in about 40% of these patients. The involvement of SMV or SV and ascites predict the failure of anticoagulation therapy [13]. A subset of patients will progress despite therapeutic anticoagulation. Certain patients with complications like bowel gangrene/perforation usually require surgical thrombectomy, with or without bowel resection. In patients with intestinal ischemia without complications of bowel perforation, transjugular local thrombolysis with or without TIPS placement is a valid therapeutic option. Klinger et al. have described a case series of 17 patients with acute non-cirrhotic and non-malignant PVT, of whom 94% were successfully treated with local therapy in the form of transjugular thrombolysis with or without TIPS placement [21]. TIPS was placed in eight patients; long term patency rates were 88% at the end of 2 years. In this study, 15/17 patients were able to avoid surgery, and none developed sequelae of portal hypertension [21]. A recent prospective study compared the role of interventional therapy (with mechanical and pharmacological thrombolysis), followed by stenting, if required, versus medical therapy. The authors reported that the former therapy was twice as effective in complete recanalization (54% vs. 30%, $p < 0.001$) but with a higher rate of bleeding complication [22]. Prospective randomized controlled trials (RCTs) between therapeutic anticoagulation and transjugular interventional therapy are required to establish the role of these therapies.

9.5.3 TIPS for Chronic Non-cirrhotic PVT

In patients with EHPVO, the recommended therapy for acute variceal bleeding is endoscopic therapy. Surgical shunts are recommended for complications, such as growth failure, symptomatic hypersplenism, portal cavernoma cholangiopathy, and recurrent variceal bleeding, despite endoscopic therapy [14, 23, 24]. Routine anticoagulation is not recommended, and only those with persistent prothrombotic state merit long-term anticoagulation after adequate prophylaxis for variceal bleed [23]. Only a few studies have evaluated the role of TIPS in this setting. Patients with EHPVO, by definition, have the presence of a portal cavernoma, which is a bunch of tortuous vessels with hepatopetal flow replacing the thrombosed main portal vein. The presence of a cavernoma causes technical difficulties in placing TIPS. Qi et al. demonstrated the feasibility and safety of TIPS in non-malignant and non-cirrhotic chronic PVT/EHPVO patients, primarily for recurrent variceal bleed [25]. Successful TIPS placement was possible in 7/20 (35%) of the patients: via a combined transjugular and transhepatic approach in 4, a combined transjugular and transsplenic approach in 2 and a transjugular approach alone in 1. Two patients required placement of TIPS within a collateral vein as the main portal vein could not

be recanalized. Shunt dysfunction occurred in 2/7 (28%) patients, and rebleeding occurred in 1 (14%) patient. None of the patients had post-TIPS encephalopathy; however, one patient had procedure-related bleed due to capsular rupture. As compared to the TIPS failure group, the rebleeding occurred in 14% (vs. 69%) patients in the TIPS success group. However, the difference in mortality was not significant due to the small sample size. In contrast, Fanelli et al., in a small study of 12 patients, reported a success rate of 83% with only one patient having shunt dysfunction and rebleed [26].

The role of TIPS in complications other than variceal bleeding has only been evaluated in one study of 28 children, of whom 17 (60%) underwent successful TIPS placement [27]. Shunt dysfunction occurred in nearly one of third patients, but a significantly higher number of patients in the TIPS success group were free of rebleeding as compared to the TIPS failure group ($p = 0.007$). The improvement in the height-for-age Z score was significantly higher in the TIPS success group as compared to the TIPS failure group ($p = 0.017$).

In view of the low technical success rate and limited availability of expertise, TIPS has a limited role in the management of patients with EHPVO. Surgical shunts, which have universally good results, are the best option. TIPS may have a role in patients not fit for surgery, but this needs to be further explored.

9.5.4 TIPS for Cirrhotic PVT

Baveno VI recommendations for the management of PVT in cirrhosis include regular 6 monthly screening in prospective transplant recipients. Institution of anticoagulation with low molecular weight heparin (LMWH) or oral anticoagulation should be done after screening for varices and appropriate pharmacological or endoscopic prophylaxis, according to the risk of variceal bleeding [23]. The basis of this recommendation in LT candidates is that the presence of advanced PVT increases the surgical complexity and leads to an increase in the rate of graft loss and mortality. Hence the main objective is to prevent thrombus progression and extension [16, 28]. The American Association of Study of Liver Diseases (AASLD) 2009 guidelines for vascular diseases of the liver do not make any recommendations for routine anticoagulation or TIPS for acute or chronic PVT in the setting of cirrhosis [29]. The European Association for the Study of the Liver (EASL) recommendations do not differ much from Baveno VI and recommend anticoagulation for at least 6 months and lifelong extension in those with an extension of the thrombus to SMV and history of intestinal ischemia or LT candidates [20]. The role in patients who are not LT candidates remains to be evaluated. A RCT by Villa et al. has shown that the use of prophylactic anticoagulation (enoxaparin) in Child B and C (B7-C10) can change the natural history of cirrhosis- at the end of 48 and 96 weeks, nearly 16% and 28% developed PVT in control group, respectively, compared with 0% and 8% in the enoxaparin group, with no increased risk of bleeding complications [30]. Patients treated with enoxaparin had lower chances of decompensation and better

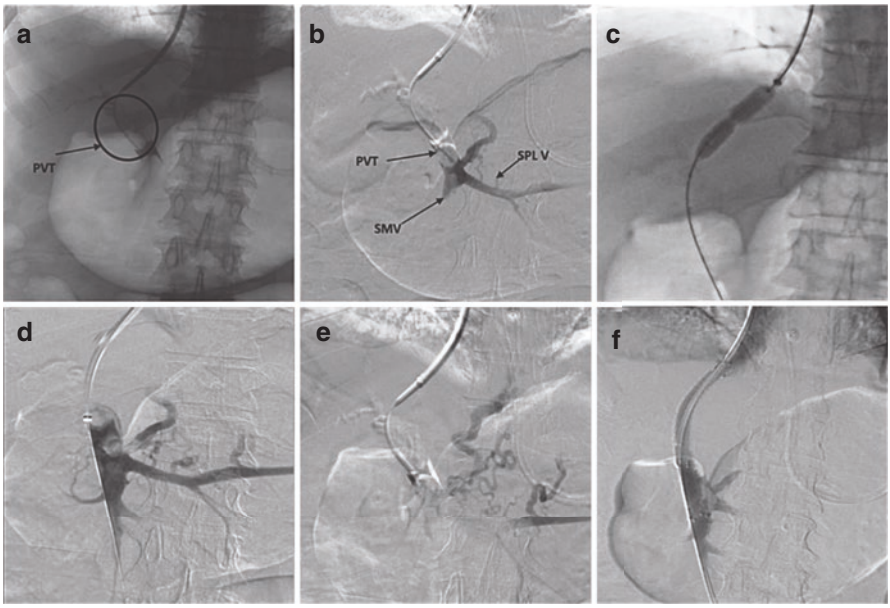

Fig. 9.3 Portogram (**a**) taken after cannulating the right portal vein showed filling defect within the main portal vein, extending till the splenoportal confluence, suggestive of thrombosis (**b**). Prior to TIPS stent placement, intraparenchymal tract was created using 10 mm × 4 cm balloon catheter (**c**). Subsequent portogram showed dilated coronary vein and varices (**d**–**e**). Final angiogram (**f**) after TIPS stent placement showed diversion of portal circulation into IVC with decompression of varices. *PVT* portal vein thrombosis, *SMV* superior mesenteric vein, *SPL V* splenic vein

survival as compared to the control group [30]. The efficacy and safety of anticoagulation with LMWH and vitamin K antagonists (VKAs) has been well established in patients with cirrhosis [31].

TIPS has been shown to be safe and effective in cirrhosis patients with PVT (Fig. 9.3). There is a lack of prospective studies comparing TIPS and anticoagulation. There might be a subgroup of patients who may not benefit from anticoagulation or be unfit for anticoagulation due to a high risk of bleeding. Luca et al. evaluated TIPS placement in 70 non-malignant cirrhotic PVT patients with a procedural success rate of 100%, among whom 57% achieved complete resolution, and 95% maintained long-term patency [32]. On follow up, only 1 in 70 had rebleeding. TIPS dysfunction was significantly higher with use of bare stents as compared to covered stents ($p = 0.0001$). In another study by Han et al., 57 patients with decompensated cirrhosis underwent TIPS primarily for variceal bleed [19]. The technical success rate was 75%, and success was dependent on the presence of cavernoma, degree of thrombosis, the involvement of portal venous branches and SMV extension. Shunt dysfunction occurred in one-fifth patients at the end of 1 year, and hepatic encephalopathy occurred in one-fourth. The rebleeding rates were significantly less in the TIPS success group compared with the TIPS failure group ($p = 0.0004$), while the survival of both groups was similar.

9.5.5 TIPS for Cirrhosis Complications

The use of TIPS in non-transplant population has also been well described. A RCT compared endoscopic band ligation and propranolol with TIPS for secondary prophylaxis of variceal bleeding in patients with cirrhosis and PVT. The authors reported a higher probability of remaining free of variceal bleeding in the TIPS group (78% vs. 43%) with no significant difference in the incidence of hepatic encephalopathy [33]. Subsequently, another trial demonstrated that in patients with cirrhosis and PVT, TIPS within 6 weeks of initial bleeding episode offered an advantage over endoscopic therapy and propranolol in terms of lower rebleeding rates at 1 year (15% vs. 45%) and at 2 years (25% vs. 50%), with no increase in encephalopathy or improvement in survival [34].

9.5.6 TIPS Procedure-Related Complications

TIPS in the setting of PVT, although technically feasible, is not without risk of complications, such as capsular perforation, hematoma, intraperitoneal hemorrhage, damage to the extrahepatic portal vein and biliary injury. Valentin et al., in their meta-analysis of 18 studies of TIPS for PVT patients with underlying liver disease, reported complications to be very rare (<1%), with only 2 cases of liver capsule perforation and hemorrhage leading to death [4]. In contrast, Rodrigues et al., in their meta-analysis of 13 studies, have reported a 10% risk of major complications [5]. Although there is a heterogeneity in complication rate, this can be explained in part by the use of catheter-related thrombolysis, which increased the complication rate to 17.7% vs. 3.3% in the TIPS alone group [5]. The complication rate of TIPS has been reported to be less when the transjugular route alone is used (5.2%), as compared to cases with transhepatic/transsplenic assistance (13.3%) [5]. The meta-analysis from Valentin et al. included studies in which the majority of patients had thrombus localized to the portal vein, and a limited number of patients had SMV or SV extension [4]. As these patients require a more invasive procedure, with more chances of complications, this might also explain the difference in complication rates between the two meta-analyses.

There is no exclusive data on post–TIPS encephalopathy, however, both the meta-analyses report hepatic encephalopathy in close to 25% during follow up.

9.6 Role of Anticoagulants Post-TIPS for PVT

There is limited evidence to support the use of anticoagulants post TIPS for PVT. In the setting of acute non-cirrhotic PVT, Klinger et al. [21] used anticoagulation with LMWH, VKA or directly acting oral anticoagulants (DOAC) for 12 months post-procedure, despite which 3/8 (37.5%) patients had a TIPS thrombosis. In the setting of chronic non-cirrhotic PVT, Qi et al. [25] used VKA, warfarin with target international normalized ratio (INR) of up to 2 for a duration of 6 to 12 months, followed

by lifelong aspirin therapy. They showed shunt dysfunction in 2/7 (28%) patients on follow up. Although anticoagulation has shown to be safe in the setting of cirrhosis, in the study by Han et al. [19] all patients received warfarin for 6–12 months followed by life-long aspirin, and they showed shunt dysfunction rate of 21%. In contrast, in the study by Luca et al. [32], none of the patients received anticoagulation, and the rate of shunt dysfunction with covered stents was 27% at 1 year.

Although LMWH and VKAs have been found to be equally effective in treating PVT, and despite its parenteral administration, LMWH is preferred over VKAs. This is because the use of INR to monitor therapeutic anticoagulation is fallacious in patients with liver disease because of the reduced synthesis of both pro and anticoagulant factors by the liver, and conversely an elevated INR increases the model for end-stage liver disease (MELD) score fallaciously, thus creating problems while listing such patients for liver transplant. In other conditions, such as renal dysfunction, VKAs are preferred over LMWH.

The role of DOACs is being explored in patients with PVT, and new data is emerging. TIPS plays an important role in the management of Budd-Chiari syndrome (BCS) [35]. TIPS is also technically feasible in BCS patients with PVT. Dabigatran has been shown to be as safe and effective in the management of post-TIPS BCS [36]. In a recent systematic review that evaluated the role of DOACs in PVT, they were found to be as effective and safe, with similar risks of major and minor bleeding episodes as traditional VKAs [37]. However, their use is offset by their cost, lack of proven safety in patients with moderate and severe hepatic and renal dysfunction and lack of cost-effective and easily available reversal agents. The issue of recommended duration of anticoagulation with DOACs has not been addressed, and various studies have used it for durations varying from 5 to 13 months [37].

9.7 Limitations of the Existing Data and Future Research

Although TIPS is feasible in the setting of PVT, yet many questions remain unanswered. The role of primary TIPS over anticoagulation alone needs to be explored in a RCT. Most studies have explored the use of TIPS after the failure of anticoagulation. The role of TIPS as compared to surgical shunts in patients with EHPVO in reducing complications, such as variceal bleeding, growth retardation, MHE, and portal cavernoma cholangiopathy, is unclear. Whether doing TIPS for PVT in the setting of cirrhosis changes the natural history of the disease and reduces further decompensation needs to be explored.

9.8 Conclusion

PVT encompasses a broad and heterogenous spectrum of abnormality. The most important distinction is to rule out the presence of underlying cirrhosis and assess the chronicity of the PVT. These subgroups have vastly different etiologies, natural history,

prognosis and treatment implications. The existing treatment recommendations support anticoagulation for a recent PVT, but recommendations for anticoagulation in chronic cases are not very clear. In a subset of patients, anticoagulation is ineffective, and TIPS has a role in further management. TIPS has been shown to effective and safe in PVT with or without cirrhosis, although there are concerns for technical difficulties in patients with chronic PVT and cavernoma. The availability of technical expertise is an important factor that determines the choice of therapy. RCTs evaluating TIPS versus anticoagulation are required to further elucidate the role of TIPS.

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