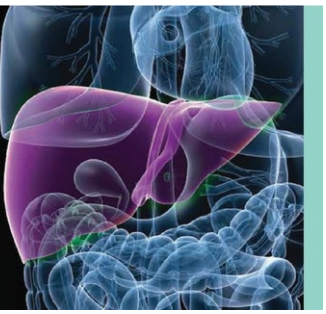

PRO: Patients With Advanced Cirrhosis and Portal Vein Thrombosis Should Receive Anticoagulation

Uyen Kim To, and Guadalupe Garcia-Tsao, M.D.*†*

KEY POINTS

- Patients with decompensated cirrhosis are relatively hypercoagulable and have higher prevalence of portal vein thrombosis (PVT).
- The natural history of PVT in patients with decompensated cirrhosis is unclear.
- Anticoagulation may provide additional benefits beyond PVT resolution.
- Current evidence does not show increased adverse outcomes in patients with cirrhosis who are anticoagulated.
- Anticoagulation is recommended in patients who are potential liver transplant candidates who have main portal vein trunk or progressive PVT.

PVT is a common problem in patients with cirrhosis.[1] The prevalence rate (using any form of imaging) ranges from 0.6% to 40%, with a higher prevalence rate in patients with decompensated cirrhosis (8%-25%) versus those with compensated cirrhosis (~1%).[1-3] In patients with compensated cirrhosis, the balance between procoagulant and anticoagulant factors is relatively stable, whereas in decompensated cirrhosis, the balance tips toward a procoagulant state.[4] In patients with decompensated cirrhosis, synthesis of anticoagulant factors such as protein C and S are decreased, and procoagulants such as factor VIII, thrombin, tissue factor, and von Willebrand factor are increased, overall resulting in a prothrombotic state.[5-8]

In compensated patients, the development of PVT is not predictive of decompensation[9]; however, in the decompensated patient, the effect of PVT on further decompensation is unclear. In patients with variceal hemorrhage, the presence of PVT is a significant independent

Abbreviations: LMWH, low molecular weight heparin; PVT, portal vein thrombosis; VKA, vitamin K antagonist.

From the *Digestive Diseases Section, Department of Medicine, Yale University, New Haven, CT; and †Digestive Diseases Section, Department of Internal Medicine, VA-CT Healthcare System, West Haven, CT.

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predictor of 5-day treatment failure, defined as rebleeding, uncontrolled bleeding, or death.[10,11] In addition, several studies show that patients with PVT who undergo hepatic transplantation have a higher morbidity and mortality post transplant. In a large cohort of patients from the Scientific Registry of Transplant Recipients from 2001 to 2007, pretransplant PVT did not affect waitlist mortality but was associated with a 32% greater risk for death (HR, 1.32; confidence interval [CI], 1.1-1.7; $P = 0.02$).[12] Although PVT can be removed surgically at the time of transplant, mortality rates have a tendency to be higher post transplant, particularly if requiring nonphysiologic portal vein reconstruction.[13] Other than posttransplant outcomes and intestinal ischemia with superior mesenteric vein thrombosis, no other clinical outcomes in cirrhosis have been clearly related to the development or presence of PVT.

Whether patients with PVT should be anticoagulated, and the duration of anticoagulation, has been controversial, especially because PVT appears to be a dynamic process. In a prospective study of 1243 patients with cirrhosis without PVT, 118 patients had PVT. Most of the PVTs were nonocclusive and resolved in 70% of cases. However, 12% progressed to occlusive thrombi with no clear predictors of thrombi progression.[9] Despite this finding, it is important to note that this study was performed in patients with compensated cirrhosis who have a lower risk for thrombotic events. The course of PVT in patients with decompensated cirrhosis remains to be determined.

Anticoagulation in patients with PVT has shown that resolution of PVT is variable. Anticoagulants evaluated in these studies have included vitamin K antagonists (VKAs) or low molecular weight heparin (LMWH). A recent meta-analysis including 12 studies of patients with cirrhosis with PVT who were treated with anticoagulation showed that 67% (95% CI, 55%-78%) had some degree of PVT recanalization, and 42% (95% CI, 29%-55%) of patients achieved complete PVT recanalization (Table 1).[14]

In addition, recent evidence suggests that anticoagulation may have benefits beyond resolution of PVT. In a randomized open-label trial of enoxaparin versus no enoxaparin in decompensated (Child B/C) patients with cirrhosis and without PVT at baseline, Villa et al.[15] showed a lower incidence of PVT in patients within the enoxaparin group. Importantly, the study also showed both a significantly lower rate of further decompensation in the enoxaparin

TABLE 1. STUDIES EVALUATING THE EFFICACY OF ANTICOAGULATION IN PATIENTS WITH CIRRHOSIS AND PVT[14,18-27]

Study	Patients (n)	Anticoagulation Type	Duration of Anticoagulation (months)	No Recanalization (n)	Partial Recanalization (n)	Complete Recanalization (n)
Amitrano (2010)[19]	28	LMWH	6	5	14	9
Delgado (2012)[20]	55	LMWH (47), VKA (8)	7	22	8	25
Francoz (2005)[21]	19	LMWH	8.1	11	0	8
Garcovich (2011)*	15	LMWH	6	8	N/A	N/A
Senzolo (2012)	35	LMWH	6	12	9	12
Cal (2013)	5	LMWH (2), VKA (3)	3	1	0	4
Chung (2014)	14	VKA	3.7	3	5	6
Risso (2014)[22†]	50	N/A	N/A	15	N/A	N/A
Chen (2015)[‡]	30	VKA	7.6	7	N/A	N/A
Wang (2016)[24§]	31	VKA	12	0	N/A	N/A
Tonon (2016)	42	LMWH	16	14	10	18
Bento (2011)[25]	28	LMWH, VKA	6	10	5	13
Naeshiro (2014)	26	LMWH	0.5	6	16	4
Werner (2013)[27]	28	VKA	12	5	12	11

*Partial or total recanalization was seen in 7 patients, but differentiation between partial and total was not reported.
†Partial or total recanalization was seen in 35 patients, but differentiation between partial and total was not reported.
‡Although 30 patients were treated, only 22 had follow-up. Partial or total recanalization was seen in 15 patients, but differentiation between partial and total was not reported.
§Partial or total recanalization was seen in 31 patients, but differentiation between partial and total was not reported.

group (11.7% compared with 59.4% in the control group; $P < 0.0001$) and a significantly lower mortality rate with enoxaparin (24% compared with 36% in the control group; $P = 0.020$), independent of PVT. The study also shows that serum bacterial s16 DNA and levels of the proinflammatory cytokine interleukin-6 were significantly lower in the enoxaparin group, suggesting that the observed beneficial effect of enoxaparin may have been because of a decrease in bacterial translocation or inflammation, factors that are known drivers of further decompensation.[15]

The possibility that enoxaparin may have effects beyond resolution of PVT has been further supported by experimental studies in rats with common bile duct ligation or carbon tetrachloride–induced cirrhosis and ascites. These studies demonstrated a significant decrease in portal pressure with enoxaparin (compared with saline-treated animals). However, the mechanism of reduction in portal pressure was not due to a decrease in portal flow but a decrease in intrahepatic resistance, which was secondary to decreased hepatic stellate cell activation (aSMA protein), decreased microthrombi formation (fibrin protein) in the liver, and decreased liver fibrosis.[16]

Despite these data and consensus recommendations to start anticoagulation in patients on the transplant list who experience occlusive or progressive PVT,[17] there is still hesitation due to concerns of bleeding complications. Current evidence does not show increased adverse outcomes in patients with cirrhosis who are receiving anticoagulation. A recent meta-analysis evaluating the effects of anticoagulation in 257 patients with cirrhosis and PVT showed no difference in major or minor bleeding between the groups who received anticoagulation versus those who did not (rate of occurrence was 11% for both groups). Notably, four of the studies included in the analysis that evaluated variceal bleeding demonstrated a lower rate of variceal bleeding in patients who received anticoagulation (2% in

TABLE 2. ADVERSE OUTCOMES REPORTED IN PATIENTS WITH CIRRHOSIS AND PVT WHO WERE TREATED WITH ANTICOAGULATION[18-28]

Study	Anticoagulation Type	Patients (n)	Child-Pugh Class A/B/C	Adverse Events Associated With Coagulation
Amitrano (2010)[19]	LMWH	28	B/C	1. Two patients with anemia secondary to portal hypertensive gastropathy requiring iron transfusion
Delgado (2012)[20]	LMWH (47), VKA (8)	55	25/21/9	1. One lower gastrointestinal bleeding 2. One obscure gastrointestinal bleeding 3. One oral bleeding after dental extraction 4. One vaginal bleeding 5. One surgical wound hemorrhage
Francoz (2005)[21]	LMWH	19	26/41/33%	1. One postprocedural bleeding
Garcovich (2011)	LMWH	15	A/B	1. None
Senzolo (2012)	LMWH	35	11/16/8	1. One cerebral bleed 2. One epistaxis 3. One variceal bleed 4. One hematuria
Cal (2013)	LMWH (2), VKA (3)	5	4/1/0	1. None
Chung (2014)	VKA	14	6/8/0	1. None
Risso (2014)[22*]	N/A	50	N/A	17% minor bleeding
Chen (2015)	VKA	30	6/17/5	1. Four with hematemesis 2. One with epistaxis 3. One with gingival bleeding
Wang (2016)[24]	VKA	31	12/17/2	1. Two gastrointestinal bleeding 2. One variceal bleed
Tonon (2016)	LMWH	42	N/A	1. One hemoperitoneum after paracentesis 2. Five nonmajor bleeding events
Bento (2011)[25]	LMWH, VKA	28	N/A	None
Naeshiro (2014)	LMWH	26	13/8/5	None
Werner (2013)[27]	VKA	28	N/A	1. One vaginal bleeding

*Details of minor bleeding were not described.

patients who were anticoagulated versus 12% in patients who were not anticoagulated; odds ratio, 0.232; 95% CI, 0.06-0.94; $P = 0.04$) (Table 2).[18]

The current consensus recommends that anticoagulation be considered in potential liver transplant candidates with thrombosis of the main portal vein trunk or progressive PVT, to reduce posttransplant morbidity and mortality.[17] If left untreated, patients with cirrhosis and PVT should undergo screening every 3 months to evaluate for progression of the PVT. Anticoagulation should be considered in those with progression of the PVT or extension into the SMV.[17] A potential algorithm of patients in whom anticoagulation should be considered is shown in Fig. 1. However, given the benefits that go beyond resolution of PVT (Fig. 2), one could even consider extending these recommendations to patients with cirrhosis who do not meet

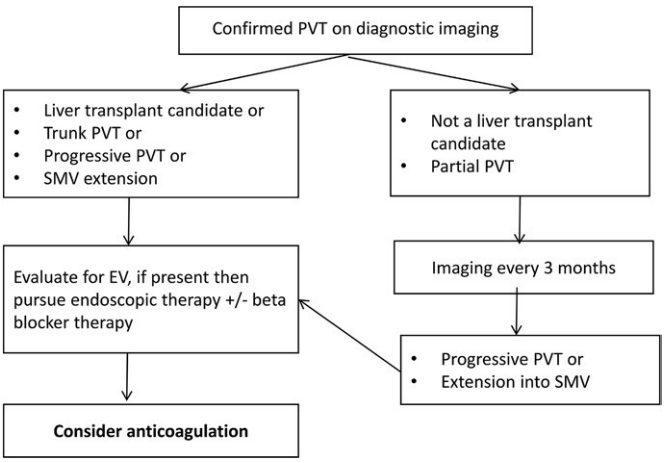

FIG 1 Potential algorithm for treatment of PVT in patients with cirrhosis.

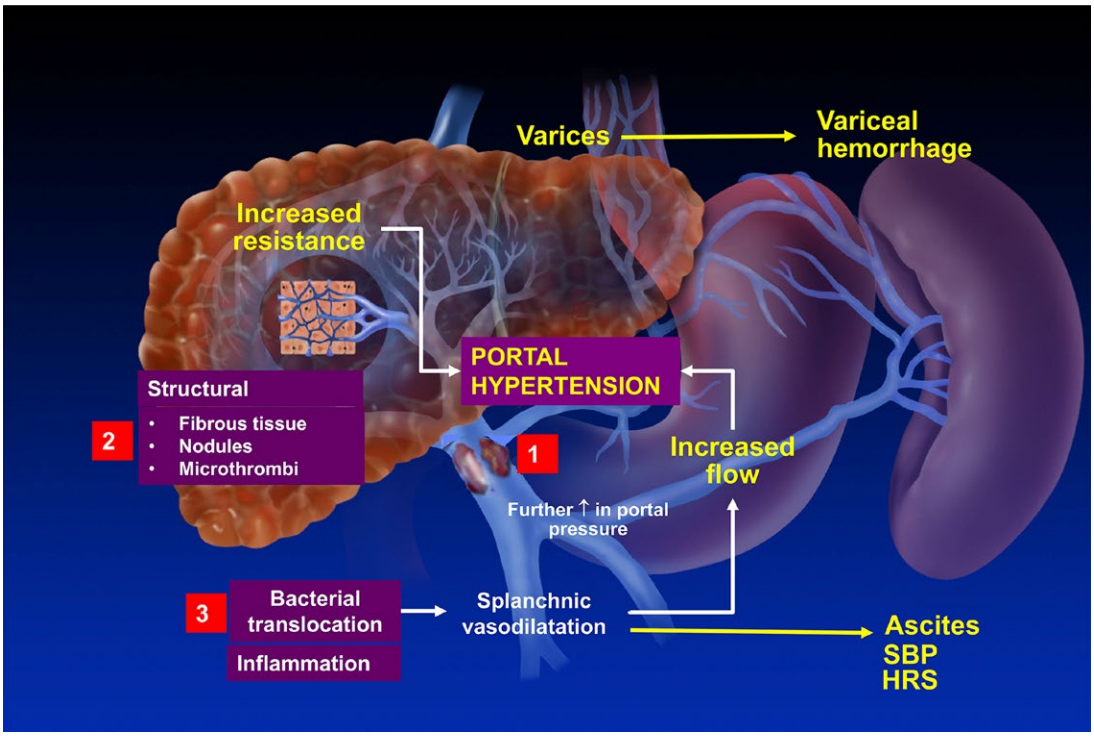

FIG 2 Pathophysiology of portal hypertension in the context of PVT and potential sites for a beneficial effect of anticoagulation. Portal hypertension in cirrhosis results from increased intrahepatic resistance and increased portal blood flow. Development of an occlusive thrombus in the main portal vein will lead to a further increase in portal pressure proximal to the site of obstruction and could potentially lead to a higher rate of variceal hemorrhage (but not to increased development of ascites). The sites at which anticoagulation could lead to better outcomes in cirrhosis are depicted in the figure: (1) Clot dissolution would decrease the proximal increase in portal vein pressure, (2) microthrombi arising from the main clot (or from the hypercoagulable state per se) could obstruct intrahepatic venules and cause an increase in sinusoidal pressure, and (3) bacterial translocation and consequent inflammation contribute to the splanchnic vasodilatation and increased portal flow that maintains the portal hypertensive state and leads to a stage of further decompensation. Abbreviations: HRS, hepatorenal syndrome; SBP, spontaneous bacterial peritonitis.

these criteria. Further studies defining the specific subpopulation of patients who benefit from anticoagulation are eagerly awaited.

CORRESPONDENCE

Guadalupe Garcia-Tsao, M.D., Professor of Medicine (Digestive Diseases), Chief, Digestive Diseases, VA-CT Healthcare System, Yale University School of Medicine, PO Box 208056, 333 Cedar Street, New Haven, CT 06520-8056. E-mail: guadalupe.garcia-tsao@yale.edu

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