Editorial

# Timing of anticoagulation for portal vein thrombosis in liver cirrhosis: An Italian internist's perspective

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Liver cirrhosis is characterized by a rebalanced hemostasis, due to a concomitantly reduced synthesis of pro-coagulant and anti-coagulant factors.[1] In this unstable hemostatic balance, patients with liver cirrhosis may easily develop spontaneous bleeding or thrombotic events.

Gastroesophageal variceal bleeding is the most feared complication and is associated with high short-term mortality rates that can reach up to 20% at 6 weeks.[2] Variceal bleeding is correlated with the severity of liver disease, the presence of portal hypertension and local factors, such as characteristics of the variceal wall. Portal hypertension can also be involved in the development of upper non-variceal gastrointestinal bleeding (portal hypertensive gastropathy) and lower gastrointestinal bleeding (portal hypertensive colopathy). Other minor bleeding events are common, frequently repeated but rarely severe, and are mainly due to primary hemostasis defects correlated with the variable degree of cirrhosis-induced thrombocytopenia: epistaxis, gingivorrhagia, purpura, and menometrorrhagia.[2]

Venous thromboembolism in cirrhotic patients can occur at any site (either deep vein thrombosis of the lower limbs, pulmonary embolism, and/or splanchnic vein thrombosis), with portal vein thrombosis (PVT) being the most frequent thrombotic event overall. The prevalence of PVT in cirrhotic patients, detected by the abdominal Doppler ultrasound in the "Portal vein thrombosis Relevance On Liver cirrhosis: Italian Venous thrombotic Events Registry" (PRO-LIVER) study, was reported to be 17%.[3] The development of PVT is correlated with the severity of the liver disease, the presence of hepatic malignancy and local factors, such as venous stasis and reduced portal flow velocity.[2] Although PVT can be asymptomatic in approximately 40% of cirrhotic patients,[3] the initial presentation can also be life-threatening with gastrointestinal bleeding, due to portal hypertension associated with PVT, or with intestinal infarction, due to thrombosis extension into the mesenteric veins.

The development of PVT has an important impact on the morbidity and mortality of cirrhotic patients. A retrospective analysis of 42 cirrhotic patients with untreated PVT showed progression of thrombus in 48% of the patients and the development of hepatic decompensation in 57% at a 2-year follow-up.[4] A meta-analysis of 3 studies comparing cirrhotic patients with and without PVT reported that PVT increased the rates of mortality (odds ratio [OR] 1.62; 95%CI, 1.11-2.36; $P$=0.01) and hepatic decompensation (OR 2.52; 95%CI, 1.63-3.89; $P$<0.001).[5] Several theories have been proposed to explain the association between PVT and the negative prognosis in liver cirrhosis, either because PVT develops more frequently in patients with severe liver failure, or because PVT further deteriorates liver function by decreasing the portal flow in a cirrhotic liver with already impaired functional reserve, or because PVT worsens the development of manifestations related to portal hypertension (such as ascites and variceal bleeding).[6,7] Furthermore,

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extensive PVT can affect the outcome of liver transplant. A systematic review reported that the presence of PVT in liver transplant recipients was associated with worse prognosis compared to patients without PVT: mortality rates at 30-day after transplant were 10.5% *versus* 7.7% respectively ($P = 0.01$), and at 1-year 18.8% *versus* 15.4% respectively ($P < 0.001$).[8] The increase in mortality post-liver transplant was particularly evident in patients with complete/occlusive PVT.[8,9] However, a retrospective analysis of 174 patients with PVT at the time of liver transplant showed that the reestablishment of physiological portal flow can cancel the differences in survival between complete and partial PVT.[10] Therefore, guidelines recommend periodic screening for PVT in patients on the waiting list for liver transplant.[11]

Anticoagulation was reported to have a positive impact on disease progression and survival in cirrhotic patients. A randomized controlled trial of 70 patients with advanced cirrhosis and patent portal vein, receiving prophylactic low molecular weight heparin (enoxaparin 4000 U daily) for one year or no treatment, showed that the antithrombotic prophylaxis not only prevented the development of PVT, but was also associated with delayed occurrence of hepatic decompensation and improved survival.[12] Furthermore, several meta-analyses reported that anticoagulation in cirrhotic patients with PVT can achieve high rates of portal vein recanalization, compared to not-anticoagulated patients, with a low incidence of major bleeding complications.[13,14] Results of a large prospective registry of SVT patients, of whom 167 had underlying liver cirrhosis, reported that these patients had the highest rates of thrombotic and major bleeding events (11.3 per 100 patient-years and 10.0 per 100 patient-years, respectively).[15] At multivariate analysis, anticoagulant treatment duration was associated with reduced risk of both thrombotic and major bleeding complications (HR 0.86, 95%CI 0.77-0.96, $P$=0.008, and HR 0.83, 95%CI 0.69-0.99, $P$=0.038, respectively).[15] Furthermore, in a small study specifically evaluating the risk of recurrent thrombotic events after VKA discontinuation, liver cirrhosis was a strong predictor of recurrence (HR 7.9, 95%CI 1.8-35.9, $P$=0.007).[16]

Although anticoagulant treatment is crucial in cirrhotic patients with SVT, the benefit/risk ratio remains particularly challenging, especially because the severity of liver disease correlates with both bleeding and thrombotic events. Several guidelines have evaluated this topic. The guidelines of the *American Association for the Study of Liver Diseases (AASLD)*, published in 2009, acknowledge that there are limited data on the benefit of the anticoagulant treatment in cirrhotic patients with PVT and, therefore, suggest that the therapeutic decision should be made on a case-by-case basis.[17] Known prothrombotic conditions or superior mesenteric vein involvement are elements that favor anticoagulation. The authors also underline the importance of adequate prophylaxis of variceal bleeding.[17] The *Baveno VI consensus*, published in 2015, recommend the consideration of anticoagulation in cirrhotic patients with PVT who are potential candidates for liver transplant, while no recommendation is made for non-candidates, thus highlighting the need for individualized treatment and for randomized trials on the benefit/risk ratio of anticoagulation in cirrhotic patients.[11] Again, elements that can shift the balance towards anticoagulation are: thrombosis extended to the superior mesenteric vein, strong prothrombotic conditions or progressive PVT. Regarding the choice of the drug, low molecular weight heparin (LMWH) and vitamin K antagonists (VKA) appear to be equally effective, while the authors recognize that data on the direct oral anticoagulants (DOACs)are scarce.[11] Finally, the guidelines of the *American College of Chest Physicians (ACCP)*, published in 2012, broadly recommend anticoagulation in patients with symptomatic splanchnic vein thrombosis (SVT) and suggest no anticoagulation in incidentally detected SVT.[18] However, this is a general recommendation, without any distinction for cirrhotic patients. Regarding the choice of drug, a preference is made for LMWH instead of VKA in patients with liver disease. Again, esophageal varices are not an absolute contraindication, because anticoagulation can reduce the complications of portal hypertension.[18]

Therefore, the currently available guidelines leave a certain degree of uncertainty in the management of cirrhotic patients with PVT. In fact, there are no randomized controlled trials specifically evaluating anticoagulation as the initial treatment of PVT, the choice of control group in cohort studies is prone to selection bias and the largest number of patients enrolled so far is 55 (in a study evaluating both LMWH and VKA).[19] However, several algorithms have been used in previous studies and can provide some guidance for the management of these patients. For instance, the study by Amitrano *et al.* assessed a regimen of LMWH only.[20] Twenty-eight patients with PVT and cirrhosis received enoxaparin 200 U/kg/die for at least 6 months. Enoxaparin was stopped after 6 months in patients with complete recanalization or with no improvement, while it was continued in patients with bowel infarct at onset or with partial recanalization on the waiting list for transplant. The timing of beginning of anticoagulation was variable: LMWH was started immediately in patients with acute abdominal pain and in asymptomatic patients with incidental finding of PVT; whereas, in those patients presenting with gastroesophageal bleeding (approximately 50% of the study cohort), LMWH was started after the endoscopic treatment of varices and prophylaxis with beta-blockers (median of 4 months from diagnosis of PVT). Complete recanalization was obtained

in 75% of anticoagulated patients in a median time of 6.5 months, without any severe bleeding event.[20] The study by Senzolo *et al.* evaluated the safety and efficacy of a therapeutic algorithm combining LMWH, at a dosage modulated on platelet count, and trans-jugular intrahepatic portosystemic shunt (TIPS).[21] The standard dose of LMWH was nadroparin 95 U/kg twice daily, but a 40% dose reduction was applied if severe thrombocytopenia (platelet count below 50,000/mm$^3$).TIPS was placed when anticoagulation was contraindicated (*e.g.*, after gastrointestinal bleeding not susceptible of endoscopic treatment) or when anticoagulation failed (*e.g.*, extension of the thrombosis despite adequate anticoagulation). LMWH was continued at prophylactic dose (3,800U/day) for 6 months after complete recanalization or longer if recanalization was not obtained or if thrombophilic abnormalities were present. Thirty-three cirrhotic patients with PVT were anticoagulated according to this protocol. Timing of starting anticoagulation was highly variable, since patients with previous variceal bleeding or with high degree varices underwent band ligation before starting anticoagulant treatment and, overall, only approximately 50% of the study cohort was started on LMWH within 6 months of PVT diagnosis. Using this anticoagulant regimen, 36% of patients obtained complete recanalization, plus an additional 27% obtained partial recanalization in a mean time of 5.5 months. One treated patient experienced a variceal bleeding *versus* 5 non-treated patients. However, among the complications related to anticoagulation, one intracranial hemorrhage has also been reported. The control group consisted of cirrhotic patients with PVT evaluated in another hospital in the same time period (between January 2007 and January 2008) and not receiving the treatment protocol.[21]

Treatment with vitamin K antagonists (VKA) has been the focus of several studies.[22-24] For instance, Francoz *et al.* evaluated the standard anticoagulant treatment, consisting of LMWH overlapped and followed by VKA (INR target range 2.0–3.0), in 19 cirrhotic patients with PVT on the waiting list for liver transplant.[22] Recanalization was significantly more common in the treated patients (42.1% *vs.* none of those not treated), but one episode of upper gastrointestinal bleeding developed. However, in this study, the treatment group consisted of patients evaluated between 1999–2001 when the local policy in the study center was anticoagulant treatment, while the control group consisted of patients evaluated at the same center between 1996–1998, who did not receive anticoagulation.[22] In the study by Chen *et al.*, 30 cirrhotic patients with PVT were anticoagulated with warfarin.[23] After adequate prophylaxis of variceal bleeding, patients were started on warfarin 2.5 mg daily and afterwards titrated to achieve INR target range 2.0–3.0. Approximately 83% of the study population started anticoagulant treatment within 3 months since PVT diagnosis. Untreated patients during the same period (between 2002–2014) constituted the control group. Recanalization was significantly more frequent in treated patients (68.2% *vs.* 25%).[23] Finally, a propensity score matching the analysis of 14 cirrhotic patients with PVT who received warfarin and 14 patients who were not anticoagulated confirmed higher rates of recanalization in the treated patients ($P$=0.022).[24]

There is limited evidence on the use of the direct oral anticoagulants (DOACs) in cirrhotic patients with PVT, since these patients were not included in the randomized controlled trials evaluating the DOACs, and since the use of the DOACs is generally contraindicated in patients with Child B and C liver cirrhosis. Several case reports described the use of rivaroxaban, administered at different dosages, in patients with mild cirrhosis and PVT.[25-27] In the literature, there are also studies evaluating different DOACs in cirrhotic patients with various indications to anticoagulant treatment, including a number of SVT patients ranging from 4 to 27,[28-30] and a series of 20 cirrhotic patients with PVT treated with edoxaban after 2 weeks of danaparoid sodium.[31] The promising results from these reports established the basis of safety and efficacy for future large studies, specifically evaluating the DOACs in cirrhotic patients with PVT.

In this context of uncertainty on the benefit/risk ratio of anticoagulation, we believe that anticoagulation in cirrhotic patients with PVT should be decided on a case-by-case basis. Since the anticoagulant treatment can prevent the progression of PVT with worsening portal hypertension and variceal bleeding, the majority of cirrhotic patients are candidates for anticoagulation during the acute phase of PVT; however, the timing might be delayed up to some weeks, due to the need to establish adequate prophylaxis of gastroesophageal variceal bleeding. Patients with low platelet count surely need more caution and may also need anticoagulant dose reduction. Underlying liver cirrhosis is a strong risk factor for recurrent events, therefore it is suggested to have an indefinite treatment duration with periodic re-assessment of the bleeding risk. LMWH and VKA(with target INR 2.0–3.0) remain the main therapeutic options for cirrhotic patients. However, INR monitoring might be difficult in patients with advanced cirrhosis and baseline prolonged INR in the absence of treatment. Vice versa, LMWH might be contraindicated if concomitant hepatorenal syndrome and requiring daily subcutaneous injections can become cumbersome for long-term treatment. There are emerging favorable data on the DOACs but they are not licensed for this indication yet. However, it should be remembered that rivaroxaban is contraindicated in patients with advanced cirrhosis (Child

class B and C), after a pharmacokinetic study showed increased rivaroxaban concentrations in patients with moderate hepatic impairment;[32,33] while apixaban has the highest percentage of hepatic metabolism (up to 73%) and therefore should be used with caution in patients with mild or moderate liver impairment (Child class A and B), it is not recommended in patients with severe liver impairment.[34,35] Anticoagulation is especially important in cirrhotic patients on the waiting list for liver transplant, since it can improve post-transplant survival.

## Conflict of Interest

Walter Ageno has received a research grant from Bayer to support a clinical study in patients with splanchnic vein thrombosis. Nicoletta Riva has no relevant conflicts to declare in relation to this paper.

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