

Title:

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Treatment of portal vein thrombosis in cirrhosis patients

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Portal vein thrombosis (PVT) is a complication in the course of liver cirrhosis, with an annual incidence ranging from 1.6 % to 26 %, depending on the cirrhosis stage of the patient cohort under study (1-5). The severity of cirrhosis and portal hypertension seems to be the most significant risk factor for the development of PVT, with other factors such as coagulation changes and persistent inflammation in splanchnic venous circulation being less clearly established (2).

The potential contribution of PVT to cirrhosis progression and a faster development of acute decompensation is controversial. With the exception of the specific scenario of acute variceal bleeding, where PVT increases the risk of early bleeding relapse (6,7), no direct relationship has been shown between PVT development and liver decompensation or death (1,3,4,8). In other words, PVT is a result of the natural history of cirrhosis rather than a factor directly contributing to cirrhosis progression. Furthermore, in contrast to PVT developing in patients without cirrhosis, in patients with cirrhosis spontaneous portal vein recanalization is common (35-50 %) (1,3,9).

Such evidence, together with the risk for bleeding diathesis in cirrhosis, has led to question anticoagulant use in the treatment of PVT in cirrhosis. In contrast, very recent evidence suggests that long-term use of anticoagulants may reduce complications rates and increase survival in patients with cirrhosis (10-13).

These facts set up a complex scenario for, while PVT seemingly does not negatively affect the natural history of cirrhosis, its treatment with anticoagulants may improve survival and prevent complications from developing. A number of questions follow this statement: should we indicate anticoagulants for all patients with cirrhosis and PVT? Is portal recanalization the goal of treatment? Should we pursue the same therapy goal in patients eligible and non-eligible for transplantation? Is treatment safe? Are all anticoagulants alike?

Current recommendations, as discussed in the Baveno VII Consensus Workshop, establish that anticoagulation is indicated in patients with cirrhosis and PVT meeting some of the following assumptions: a) PVT is recent (< 6 months); b) the thrombus occupies less than 50 % of the vessel's lumen, whether the superior mesenteric vein is involved or otherwise; and c) the patient is eligible for liver transplantation (regardless of occlusion degree and extent) (14). These recommendations are based on retrospective cohort studies and several meta-analyses of aggregate data, which observed that anticoagulation increases 3-fold the likelihood of portal recanalization, especially if initiated within 6 months after PVT onset (11,15,16). Long-term anticoagulation, even beyond recanalization itself, would be useful to prevent rethrombosis, which occurs in up to one third of patients once treatment has been discontinued (17). These recommendations become particularly relevant in patients eligible for liver transplantation, since in them it is key that portal recanalization is fostered and progression to thrombosis is avoided to allow for physiological vascular anastomoses during transplantation (18,19). However, the benefit of anticoagulation in patients not eligible for transplantation or with less severe PVT is more controversial, and the Baveno VII Consensus Workshop only went so far as to individualize the decision to anticoagulate as reflected by the figure 1.

The recent publication of a meta-analysis of data from 500 individuals with PVT, comparing those treated versus those not treated with anticoagulation, has allowed to

answer some of the above questions (20). First off, the study shows that anticoagulation decreases all-cause mortality in patients with cirrhosis and PVT, with a hazard ratio (HR) of 0.59 (95 % CI, 0.49-0.70), an effect that is independent of cirrhosis severity and that remains long-term, even after discontinuing anticoagulation. Secondly, while anticoagulation increases the likelihood of recanalization 3.5-fold, the benefit on survival occurs regardless of its achievement. Lastly, this benefit is also independent of portal vein occlusion degree, whether partial or complete. Thus, the study concludes that PVT identifies a group of patients with cirrhosis who would benefit from receiving anticoagulants long-term.

Anticoagulation safety in patients with cirrhosis has always been a focus of interest. Cumulative evidence with vitamin K antagonists (VKAs) and low molecular weight heparins (LMWHs) suggests that these drugs are safe for patients with cirrhosis and PVT. In fact, the estimated incidence of severe bleeding is 2.8 % (95 % CI: 1.4-4.6), with no differences between anticoagulated and non-anticoagulated patients in an aggregate data meta-analysis, and is similar to that of patients with cirrhosis without PVT (2.0 % (95 % CI: 1.0-3.3) (21,22). However, an individual data meta-analysis has allowed a more accurate interpretation of the data, showing that anticoagulation in cirrhosis increases the risk for upper GI bleeding unrelated with portal hypertension (20). These results, which are similar to those of patients without cirrhosis on anticoagulants, reinforce the overall recommendation of assessing and treating potentially modifiable bleeding risk factors before anticoagulation onset. To be highlighted in this population is adequate primary and secondary prevention of variceal bleeding using non-cardioselective beta-blockers and endoscopic band ligation, according to established recommendations (14).

To date, LMWHs and VKAs have been the most commonly used anticoagulants in the treatment of PVT in cirrhosis. LMWHs such as enoxaparin are usually given at an initial dose of 1.5 mg/kg/day, that is then down-titrated to 1.0 mg/kg daily for up to 2-3 months, after which VKAs are used. The latter are used for long-term PVT treatment with a target INR between 2.0 and 3.0, although cirrhosis-related coagulation changes prevent establishing whether this therapeutic range is optimal for these individuals. In a small series of patients with cirrhosis and PVT who were treated with VKAs, a platelet

count $< 50,000/\mu\text{l}$ was associated with a higher bleeding risk, hence their use should be avoided in such cases (23). Similarly, no safety information is available regarding patients with extreme thrombopenia (platelet count $< 30,000/\mu\text{l}$), and therefore it is recommended that anticoagulation be withheld in these patients. Since their introduction over a decade ago, direct-acting oral anticoagulants (DOACs) have gradually replaced VKAs and LMWHs in most indications, but their use in cirrhosis remains controversial. In fact, experience with their use in cirrhosis is restricted to Child-Pugh A and B patients, as they are formally contraindicated in those with Child-Pugh C. A network meta-analysis in patients with cirrhosis and PVT has shown that DOACs are more effective than LMWHs and VKAs in achieving complete portal vein recanalization, with similar bleeding rates (24). Regarding safety, DOACs have a similar or even better risk profile when compared to VKAs, as was shown in an aggregate data meta-analysis of patients with cirrhosis who were treated VKAs and DOACs (mostly apixaban and rivaroxaban) (25). In fact, a cohort study of American veterans with cirrhosis (mostly with Child-Pugh A) treated with VKAs or DOACs for nonvalvular atrial fibrillation has shown a lower, usually digestive bleeding rate, in patients on DOACs, with a HR of 0.49 (95 % CI: 0.26-0.94) (13). These results describe DOACs as safe, likely first-choice drugs for patients with compensated cirrhosis. Given the hepatic metabolism and renal clearance of DOACs, their use in patients with Child-Pugh B or glomerular filtration rate $< 30 \text{ mL/min}$ must be cautious and requires dose titration (14). Finally, while each DOAC has its own, different safety and effectiveness profile, in the cirrhosis setting no comparative studies are available to support any of them specifically.

To conclude, PVT is an uncommon event in the natural history of cirrhosis. While no strong evidence is available, anticoagulation is indicated for some groups of patients where the severity of portal occlusion or eligibility for transplantation require that portal recanalization be attempted. Beyond recanalization, anticoagulation, at least in patients with PVT, seems to have a beneficial effect on the natural history of cirrhosis, which raises concern on the opportunity for discontinuation once cirrhosis sets in. In any case, the potential benefit must be assessed on a case by case basis considering the higher bleeding risk any patient on anticoagulation runs. Let us hope that the

evidence generated in the upcoming years will provide a response to these questions.

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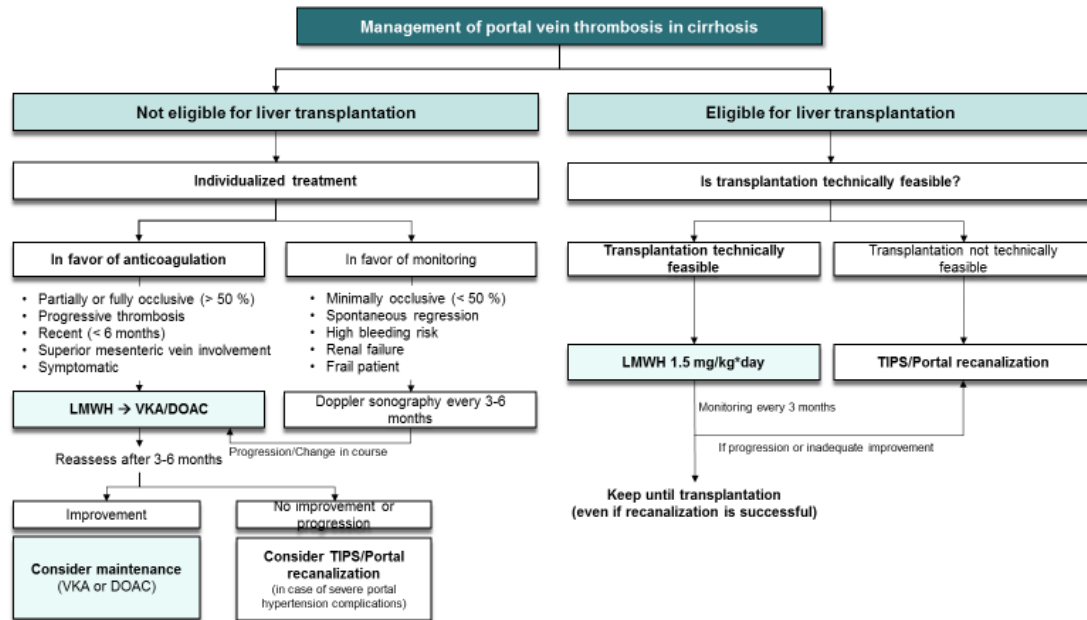


Fig. 1. Management of portal venous thrombosis in patients with liver cirrhosis (DOAC: direct-acting oral anticoagulant; VKA: vitamin K antagonist; LMWH: low molecular weight heparin; TIPS: transjugular intrahepatic portosystemic shunt).



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