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Anticoagulant Therapy for Splanchnic Vein Thrombosis

ISTH SSC Subcommittee Control of Anticoagulation

Running head: Management of splanchnic vein thrombosis

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Scope and methodology

Splanchnic vein thrombosis is an unusual site venous thromboembolism (VTE) which includes portal, mesenteric, or splenic vein thrombosis, and the Budd-Chiari syndrome.[1, 2] The management of splanchnic vein thrombosis remains challenging and often empirical with limited evidence from observational studies and few small randomized trials.[1, 2]

The scope of this guidance document is to provide clinicians with practical advice on how to manage splanchnic vein thrombosis, identify patients who may benefit of anticoagulant treatment, and decide on the type and duration of anticoagulation.

A systematic search of the literature was performed in MEDLINE and EMBASE databases, and clinical trial registries were searched to retrieve additional information from ongoing studies. Selected articles were critically appraised to formulate guidance statements on relevant clinical questions.

The wording "recommend" indicates a strong guidance statement with good consensus among the panelists, whereby the clinician should consider adopting the practice in most cases. The wording "suggest" reflects a weak guidance statement with moderate consensus among the panel members, whereby the clinician may adopt the guidance statement or use an alternative approach to manage patients.

Background

The incidence of splanchnic vein thrombosis is about 25 times lower than usual site VTE (i.e. deep vein thrombosis and pulmonary embolism) and varied broadly across different studies with the most and least common types represented by portal vein thrombosis and Budd-Chiari syndrome, respectively.[2-5] Liver cirrhosis, solid cancer, and myeloproliferative neoplasms represent the three major risk factors for splanchnic vein thrombosis.[6-8] Transient risk factors such as surgery, abdominal inflammation/infection, or hormonal replacement therapy may also be associated with splanchnic vein thrombosis, which remains unprovoked in up to one fourth of cases.[6, 7] A large prospective registry found a close relationship between underlying risk factors and prognosis of splanchnic vein thrombosis. Patients with thrombosis due to transient risk factors had the lowest risk of thrombotic (3.2 per 100 patient-year) and major bleeding (0.5 per 100 patient-years) complications, whereas patients with underlying chronic major risk factors like liver cirrhosis had the highest incidence of events (11.3 and 10.0 per 100 patient-year, respectively).[7]

Splanchnic vein thrombosis is associated with high mortality, especially during the first month after diagnosis and in case of mesenteric vein involvement, but risk remains significant up to 5 years in patients with portal and hepatic vein thrombosis.[9]

Treatment evaluation

The use of anticoagulant treatment for splanchnic vein thrombosis has been associated with significant reduction of thrombotic events and major bleeding compared with no anticoagulation.[7] Early administration of anticoagulants within the first two weeks after diagnosis may lead to better vessel recanalization.[10,11] The decision to start and the optimal timing of anticoagulant treatment have to be balanced against the risk of bleeding, mostly gastrointestinal, which may be relevant because of the acute manifestation of splanchnic vein thrombosis which includes venous intestinal congestion, the concomitant comorbidities, and the presence of gastroesophageal varices. An immediate evaluation by a surgical team is critical in patients with severe clinical presentation (e.g. shock, peritonitis, perforation, intestinal infarction or acute major gastrointestinal bleeding) before considering anticoagulant treatment. An interdisciplinary discussion should take place to inform of any plans for surgery or invasive procedures so that anticoagulant treatment is avoided at that time. Prior to anticoagulation, clinicians should consider performing esophagogastroduodenoscopy for variceal screening in selected patients at risk of portal hypertension, medical prophylaxis with beta-blockers, and endoscopic variceal band ligation for high-risk varices to reduce the incidence of first and recurrent variceal bleeding.[12-14] After medical prophylaxis and endoscopic treatment, the risk of bleeding seems comparable between patients with splanchnic vein thrombosis receiving anticoagulant treatment and those who are left untreated.[14] Endoscopic band ligation may require multiple attempts which could delay the start of anticoagulation. Preliminary data suggest that commencing anticoagulation within two weeks after variceal band ligation may still achieve significant vein recanalization without increasing the incidence and severity of bleeding nor affecting the efficacy of variceal eradication.[14-16]

Based on currently available evidences, a suggested approach to manage patients with splanchnic vein thrombosis is outlined in Figure. The panel acknowledges that the available evidence on the management of splanchnic vein thrombosis is mainly derived from observational studies and, therefore, the level of evidence should be considered weak for all recommendations.

Acute splanchnic vein thrombosis

Acute splanchnic vein thrombosis is generally defined as thrombosis involving one or more splanchnic veins without evidence of portal cavernoma or collateral portosystemic circulation.[2] Treatment of occlusive or non-occlusive acute splanchnic vein thrombosis aims to prevent intestinal infarction or ischemia, and achieve the highest possible vessel recanalization to reduce splanchnic hypertension and bleeding risk.[17]

Most data on the treatment of acute splanchnic vein thrombosis come from studies on patients with liver cirrhosis. In a recent trial of 65 cirrhotic patients with portal vein thrombosis receiving 6-month therapeutic dose low molecular weight heparin (LMWH), 78.5% achieved complete (26.2%) or partial (52.3%) recanalization, 9.2% had thrombosis progression, and none experienced variceal bleeding.[12] Similar recanalization rates were reported in two prospective cohorts of cirrhotic patients of whom most had an acute or progression of a previous splanchnic vein thrombosis.[10, 18] In a randomized controlled trial of 80 cirrhotic patients with portal vein thrombosis after splenectomy, rivaroxaban (10 mg bid) was compared with warfarin (therapeutic range, international normalized ratio [INR] 2.0 to 2.5).[19] Rivaroxaban was associated with higher complete (85.0% vs. 45.0%) or partial (15.0% vs 0%) recanalization rates. In addition, recurrent portal vein thrombosis after treatment discontinuation and major bleeding occurred only in warfarin-treated patients (10.0% and 42.5%, respectively).[19] These findings, however, need to be interpreted with caution due to the small size of the study, risk of bias, and the potential for residual confounding.

The evidence on the treatment of acute splanchnic vein thrombosis in patients without liver cirrhosis is sparse. In a prospective cohort of 95 patients with splanchnic vein thrombosis unprovoked or secondary to myeloproliferative neoplasm or thrombophilia, treatment with vitamin K antagonists (VKAs) achieved vein recanalization in 38%, 54%, and 61% of patients with portal, mesenteric, and splenic vein thrombosis, respectively.[16] Bleeding requiring blood transfusion or hospital admission developed in 5.3%.[16] Use of anticoagulant therapy for longer than 6 months seemed to further improve vein recanalization in patients with mesenteric or splenic thrombosis, but not in those with portal vein thrombosis. In a retrospective study of 375 patients with acute splanchnic vein thrombosis and various underlying risk factors, the incidence of recurrent VTE (0.77 per 100 patient-years) and major bleeding (1.24 per 100 patient-years) was low during a median 2-year treatment with VKAs.[20] Higher rates of thrombotic events (5.6 per 100 patients-years) and major bleeding (3.9 per 100 patients-years) were reported during treatment in a large

prospective registry of 604 patients with recent splanchnic vein thrombosis of whom 77.0% received anticoagulant therapy.[7] The large variation in the rates of thrombotic or bleeding complications observed across studies may be related to differences in anticoagulant regimens, management of VKAs, outcome definitions, or characteristics of study populations.

High recanalization rates with anticoagulation have been observed also for acute splanchnic vein thrombosis secondary to abdominal inflammation or infection, inflammatory bowel disease, general or bariatric surgery.[21-24]

The role of systemic or catheter-directed thrombolysis has been evaluated only in small case-series which reported promising results mostly in terms of vein recanalization, but a high risk of major and fatal bleeding.[25-29] Based on these preliminary observations, thrombolysis may be carefully evaluated in specialized centers for very selected patients such as those with clinical deterioration despite anticoagulant therapy.

Since specific treatment for splanchnic vein thrombosis was not mandatory in most studies, the choice of anticoagulant agent and intensity of anticoagulation have been highly heterogeneous. LMWH either alone or in combination with VKAs were evaluated in observational studies that were often small, retrospective, and with a high risk of bias.[2,30] The evidence on oral anticoagulants directly inhibiting thrombin (dabigatran) or activated factor X (rivaroxaban, apixaban, and edoxaban) is very limited. Direct oral anticoagulants (DOACs) have shown similar efficacy and better safety compared with VKAs in patients with usual site acute VTE and are the current recommended first line treatment. A similarly favorable risk-benefit profile of DOACs may be expected in patients with splanchnic vein thrombosis. In contrast with LMWH or VKAs, DOACs may have a pronounced first-pass effect that could result in high concentrations of these agents at site of splanchnic vein thrombosis with standard concentrations in the periphery. The potential for DOACs malabsorption needs to be considered in cases complicated by bowel ischemia.

The type and dose of anticoagulant treatment may need frequent adjustments according to a number of patient comorbidities such as low platelet count, liver and renal impairment.[2] LMWH alone may be preferable in patients with moderate to severe impairment of liver function as the latter may negatively affect the quality of anticoagulation with VKAs. The use of DOACs is contraindicated in case of moderate (rivaroxaban) or severe (all DOACs) liver dysfunction. In most countries, the use of DOACs remains off-label in patients with splanchnic vein thrombosis regardless of the presence of cirrhosis.

Another advantage of LMWH is the possibility to adapt doses in patients with thrombocytopenia or recent bleeding. LMWH have shown better efficacy and similar safety compared with VKAs in patients with cancer and VTE, and their use may be considered in cases of splanchnic vein thrombosis and underlying malignancy.[31] In patients with gastrointestinal cancer, the use of DOACs (edoxaban and rivaroxaban) was associated with increased risk of gastrointestinal bleeding compared with LMWH. The SSC guidance of the ISTH suggests treatment with LMWH in cancer patients with VTE who have luminal gastrointestinal malignancy, active gastrointestinal mucosal abnormalities, genitourinary cancer at high risk of bleeding, or are receiving systemic therapy with potential drug-drug interactions with DOACs.[32]

The optimal duration of anticoagulant treatment for splanchnic vein thrombosis remains unclear. Most studies have provided anticoagulation for 6 months or longer.[7,10,12,14,18-20] Extended treatment duration beyond 6 months may be beneficial in subgroups at high risk such as those awaiting liver transplantation with the aim of lowering the risk of vein thrombosis recurrence or progression.[10,18,20,33] Other patient groups who may benefit from longer anticoagulation include those with history of intestinal ischemia, thrombosis extending beyond the portal vein, thrombosis recurrence or progression after treatment discontinuation, unprovoked thrombosis, or thrombosis associated with a persistent risk factor, such as severe inherited thrombophilia or myeloproliferative neoplasms.[7,10,16,18,19,34] In this latter case, cytoreduction appeared not to reduce recurrent thrombosis.[35] The evidence to guide anticoagulant treatment duration based on the rate of vein recanalization remains limited.[14,18,19]

Chronic splanchnic vein thrombosis

Chronic splanchnic vein thrombosis is generally defined by the presence of signs of long-standing thrombosis such as extensive intra-abdominal venous collaterals or cavernous transformation of the portal vein.[2]

The age of the thrombus can only be approximated by the clinical course of symptoms or the time interval between the first imaging procedure demonstrating splanchnic vein thrombosis and previous radiological imaging with no signs of thrombosis, if available.[14] The clinical relevance of chronic splanchnic vein thrombosis remains uncertain and the decision to initiate anticoagulant therapy should also consider patient preferences, the effects on quality of life, and costs. The main objectives of anticoagulant therapy for chronic splanchnic vein thrombosis are the prevention of recurrent thrombosis as well as vessel recanalization, although the latter tends to be less impacted

by treatment compared to recanalization in patients with acute thrombosis.[2,14,24,36] Therapy may be considered in selected patients in whom the risk of recurrence is judged to outweigh that of bleeding. A watchful approach or lower intensity anticoagulation may still be considered in some cases to minimize the risk of bleeding. In two retrospective studies including mostly patients with chronic splanchnic vein thrombosis, anticoagulant treatment with LMWH and VKAs tended to reduce recurrent thrombosis compared with no treatment.[13,37] Data on the risk of bleeding were conflicting as one study showed a tendency for lower rates with anticoagulation,[13] while the other cohort suggested a twofold higher risk.[37]

A longer course of anticoagulant treatment may be considered in patients who remain at risk of recurrence such as those with unprovoked thrombosis or persistent thrombotic risk factors.[13,14, 36, 37] Preliminary evidence suggests that prophylactic dose LMWH may be effective in preventing thrombosis progression compared with no treatment (14.3% vs. 71.4%).[14] The intensity and need for anticoagulant treatment require periodic reevaluations to ensure a favorable risk-benefit profile.

Incidental splanchnic vein thrombosis

Splanchnic vein thrombosis is incidentally diagnosed during abdominal imaging in up to one third of cases.[38,39] Patients with incidentally detected splanchnic vein thrombosis tend to be older than those with symptomatic SVT and often have persistent thrombotic risk factors such as liver cirrhosis or solid cancer.[38]

The incidence of recurrence, progression or extension of thrombosis appears similar to that of symptomatic splanchnic vein thrombosis, with the highest risk in patients with liver cirrhosis or solid cancer.[38,39] Anticoagulant treatment reduces thrombotic events and does not seem to increase major bleeding compared with no treatment.[38,39]

Budd-Chiari syndrome

Budd-Chiari syndrome is the least common type of splanchnic vein thrombosis which may involve different vein segments from the small hepatic venules up to the inferior vena cava. Most patients have a myeloproliferative neoplasm or thrombophilia as underlying risk factors.[40-42]

All patients with Budd-Chiari syndrome should undergo endoscopic evaluation to verify the presence of gastroesophageal varices which may require specific treatment to lower the risk of gastrointestinal bleeding.[41,43] Both anticoagulant therapy and invasive procedures (i.e.,

thrombolysis, percutaneous transluminal angioplasty, trans-jugular intrahepatic portosystemic shunting, surgical portosystemic shunting, and orthotopic liver transplantation) have been used for Budd-Chiari syndrome.[40,42-44] A stepwise approach was proposed which includes long-term anticoagulant therapy with LMWH and VKAs followed by invasive procedures in case no clinical and laboratory response is observed within two weeks of anticoagulation.[42] Patients managed with anticoagulant therapy alone had 40% 5-year survival, 55% 1-year failure rate, and 23% developed bleeding complications.[42] Using the stepwise approach, the overall 1 and 5-year survival rates were 96% and 89%, respectively.[41,42] Since the use of invasive procedures in addition to anticoagulant treatment may increase the risk of major bleeding compared to anticoagulant therapy alone, some authors suggest to reduce anticoagulation intensity during invasive therapy to improve the risk-benefit ratio.[44] In a recent retrospective cohort of 119 patients with Budd-Chiari syndrome, anticoagulant therapy with VKAs (69.7%) or the direct thrombin inhibitor dabigatran (30.3%) was started after percutaneous intervention therapy. Use of dabigatran was limited to patients with VKAs failure defined as labile INR, difficult follow-up or bleeding during VKAs. At 18-month follow-up, there were no significant differences between dabigatran and VKAs in terms of stent patency (91% and 93%), major bleeding (3% and 6%, respectively), and survival (87% and 95%, respectively).[45]

Guidance statements

1. In patients with acute splanchnic vein thrombosis presenting with shock, high lactate levels or signs of peritonitis, perforation, intestinal infarction or acute major gastrointestinal bleeding we recommend immediate surgical evaluation and treatment before anticoagulation is introduced
2. In patients with symptomatic acute splanchnic vein thrombosis who have no active bleeding or other contraindications, we recommend to start early anticoagulant treatment
3. In patients with splanchnic vein thrombosis who have or are considered to be at risk of portal hypertension, we recommend early esophagogastroduodenoscopy for variceal screening followed by adequate medical prophylaxis and endoscopic variceal band ligation of high-risk varices
4. In patients with symptomatic acute splanchnic vein thrombosis we recommend against the routine use of systemic or catheter-directed thrombolysis. We suggest to consider the use of thrombolysis in specialized centers for very selected patients such as those with

mesenteric or extensive splanchnic vein thrombosis and signs of intestinal ischemia, or those whose conditions deteriorate despite adequate anticoagulant therapy

5. In non-cirrhotic patients with symptomatic acute splanchnic vein thrombosis who have no signs of active bleeding, we suggest full therapeutic dose of DOACs, and consider LMWH and VKAs with INR range of 2.0 to 3.0 in patients who cannot tolerate or have contraindications for DOACs. This panel acknowledges the fact that none of the anticoagulants are specifically approved for the treatment of splanchnic vein thrombosis
6. In patients with cancer-associated symptomatic acute splanchnic vein thrombosis, we recommend LMWH or DOACs. We suggest LMWH in patients with luminal gastrointestinal cancer, active gastrointestinal mucosal abnormalities, genitourinary cancer at high risk of bleeding, or receiving current systemic therapy with potentially relevant drug-drug interactions with DOACs
7. In cirrhotic patients with symptomatic acute splanchnic vein thrombosis, we suggest therapeutic dose LMWH, and switch to VKAs or DOACs if not contraindicated by severity of liver dysfunction
8. In patients with symptomatic acute splanchnic vein thrombosis and creatinine clearance < 30 ml/min, we recommend initial treatment with unfractionated heparin, apixaban, rivaroxaban, or half therapeutic dose LMWH; we suggest unfractionated heparin if creatinine clearance < 15 ml/min
9. In patients with symptomatic acute splanchnic vein thrombosis and high risk of major bleeding, we suggest to consider individualized dose reduction or delayed treatment, and suggest withholding anticoagulation in patients with poor short-term prognosis
10. In patients with symptomatic acute splanchnic vein thrombosis, we recommend the use of anticoagulant therapy for at least 3 to 6 months, irrespective of thrombosis extension and underlying risk factors
11. We recommend longer courses of anticoagulation or indefinite anticoagulant treatment in patients with thrombosis progression or recurrence after treatment discontinuation, unprovoked splanchnic vein thrombosis, or persistent risk factors. This panel acknowledges the fact that reduced doses of LMWH or DOACs may be used to minimize bleeding risk as for usual site venous thromboembolism

12. In patients with chronic splanchnic vein thrombosis, we recommend to carefully evaluate the use of anticoagulant therapy on a case-by-case basis and consider a watchful approach in selected patients to minimize bleeding
13. In patient with incidentally detected splanchnic vein thrombosis, we suggest the same treatment as for symptomatic acute splanchnic vein thrombosis
14. In patients with Budd-Chiari syndrome, we suggest indefinite anticoagulant treatment with LMWH, DOACs if not contraindicated by liver dysfunction, or VKAs with INR range of 2.0 to 3.0 in selected patients who cannot tolerate or have contraindications for DOACs
15. We recommend physicians to regularly reassess the thrombotic and bleeding risk to decide on the intensity and need for anticoagulant therapy

Authors' contribution

Concept and design: M. Di Nisio, E. Valeriani, W. Ageno. Interpretation of data, critical writing or revising the intellectual content, and final approval of the version to be published: All authors.

Conflict of interest

M. Di Nisio reports personal fees from Bayer, Daiichi Sankyo, Pfizer, Leo Pharma, and Aspen, outside the sub- mitted work; E. Valeriani and N. Riva have no conflict of interest to declare; S. Schulman received grants and personal fees from Boehringer Ingelheim, Octapharma as well as personal fees from Bayer, Daiichi Sankyo, Pfizer, Alnylam, and Sanofi outside the submitted work; Jan Beyer-Westendorf has received honoraria and research support from Bayer HealthCare, Boehringer Ingelheim, Daiichi Sankyo, Pfizer and Portola. S.M. has received honoraria from

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Figure – Treatment evaluation in patients with splanchnic vein thrombosis