**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 86612

**Manuscript Type:** REVIEW

**Direct oral anticoagulants for the treatment of splanchnic vein thrombosis: A state of art**

Monaco G *et al*. DOACs for splanchnic vein thrombosis

Giovanni Monaco, Luca Bucherini, Bernardo Stefanini, Fabio Piscaglia, Francesco Giuseppe Foschi, Luca Ielasi

**Giovanni Monaco, Bernardo Stefanini, Fabio Piscaglia,** Department of Medical and Surgical Sciences, University of Bologna, Bologna 40138, Italy

**Giovanni Monaco, Bernardo Stefanini, Fabio Piscaglia,** Division of Internal Medicine, Hepatobiliary and Immunoallergic Diseases, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna 40138, Italy

**Luca Bucherini, Francesco Giuseppe Foschi, Luca Ielasi,** Department of Internal Medicine, Ospedale degli Infermi di Faenza, Faenza 48018, Italy

**Author contributions:** Monaco G, Bucherini L, Stefanini B and Ielasi L conceived the manuscript, reviewed the literature and wrote the original draft; Monaco G and Ielasi L reviewed and edited the manuscript; Piscaglia F and Foschi FG supervised; All authors read and agreed to the published version of the manuscript.

**Corresponding author: Luca Ielasi, MD, Doctor,** Department of Internal Medicine, Ospedale degli Infermi di Faenza, Viale Stradone, 9, Faenza 48018, Italy. luca.ielasi.kr@gmail.com

**Received:** June 27, 2023

**Revised:** August 7, 2023

**Accepted:** August 17, 2023

**Published online:** September 7, 2023

**Abstract**

Splanchnic vein thrombosis (SVT) is a manifestation of venous thromboembolism in an unusual site. Portal, mesenteric, and splenic veins are the most common vessels involved in SVT which occurs mainly in patients with liver cirrhosis, although non-cirrhotic patients could be affected as well. Thrombosis of hepatic veins, also known as Budd-Chiari syndrome, is another manifestation of SVT. Prompt diagnosis and intervention are mandatory in order to increase the recalization rate and reduce the risk of thrombus progression and hypertensive complications. Traditional anticoagulation with heparin and vitamin-K antagonists is the treatment of choice in these cases. However, recent studies have shown promising results on the efficacy and safety of direct oral anticoagulants (DOACs) in this setting. Available results are mainly based on retrospective studies with small sample size, but first clinical trials have been published in the last years. This manuscript aims to provide an updated overview of the current evidence regarding the role of DOACs for SVT in both cirrhotic and non-cirrhotic patients.

**Key Words:** Splanchnic vein thrombosis; Portal vein thrombosis; Budd-Chiari syndrome; Direct oral anticoagulants

**©The** **Author(s) 2023.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation:** Monaco G, Bucherini L, Stefanini B, Piscaglia F, Foschi FG, Ielasi L. Direct oral anticoagulants for the treatment of splanchnic vein thrombosis: A state of art. *World J Gastroenterol* 2023; 29(33): 4962-4974

**URL:** <https://www.wjgnet.com/1007-9327/full/v29/i33/4962.htm>

**DOI:** https://dx.doi.org/10.3748/wjg.v29.i33.4962

**Core Tip:** The term splanchnic vein thrombosis (SVT) includes portal vein thrombosis and Budd-Chiari syndrome. Both conditions could occur in patients with and without an underlying liver disease. The cornerstone of treatment is anticoagulation. Direct oral anticoagulants (DOACs) are a novel class of drugs that have strongly affirmed their role in the management of patients with atrial fibrillation and venous thromboembolism. In the last few years, several studies have been published showing promising results in efficacy and safety of DOACs in patients with SVT.

**INTRODUCTION**

Splanchnic vein thrombosis (SVT) is a rare but potentially life-threatening condition that occurs when blood clots form in the veins that drain the digestive system from the lower esophagus to the upper two-thirds of the rectum. Among different SVT, we can distinguish two main conditions: Budd-Chiari syndrome (BCS) and portal vein thrombosis (PVT).

BCS is caused by the thrombotic obstruction of hepatic venous outflow, localized anywhere from the hepatic veins to the entry of the inferior vena cava into the right atrium. BCS could also be caused by extra-vascular compression (secondary BCS), but this non-thrombotic form of the disease will not be discussed further.

There is no standardized definition of PVT. Generally, it refers to the thrombosis of the main portal trunk or its lobar branches with or without extension to the splenic or mesenteric veins.

SVT can develop both in patients with and without underlying liver disease[1].

In the first case, SVT represents a rare condition with a prevalence of less than 0.2% in the general population and it is commonly associated with strong risk factors for thrombosis[2].

In the second case, liver cirrhosis represents the mainstay of the pathogenesis of SVT and the co-presence of thrombophilic risk factors is uncommon. Cirrhotic patients generally present a PVT with an incidence that ranges from 11% to 24% at 5 years; prevalence increases according to liver disease severity (10% in compensated cirrhosis, 17% in decompensated cirrhosis, and 26% in liver transplant candidates)[3-5].

In patients with SVT, the development of portal hypertension is common; the increase of portal venous pressure could be caused by either pre-hepatic (in PVT) or post-hepatic (in BCS) venous flow obstruction.

As a thrombotic condition, anticoagulation is generally required for these patients as first line treatment. Over the last few years, interventional endovascular approaches (*e.g.* transjugular intrahepatic portosystemic shunt placement, angioplasty, suction thrombectomy, catheter-directed thrombolysis) have shown interesting results mainly in the management of acute symptomatic PVT with an inadequate response to medical treatment[6-8]. They could be used in isolation or in conjunction with systemic anticoagulation. Description of these procedures and their indications go beyond the aim of this paper, so it will not be discussed further.

Traditional anticoagulants commonly used for SVT are heparins and vitamin-K antagonists (VKA).

Low-molecular-weight heparin (LMWH) is generally preferred to unfractionated heparin (UFH) due to its lower incidence of heparin-induced thrombocytopenia, unless there are contraindications to LMWH such as severe renal failure. LMWH also has the advantage that it has a short half-life and no need of monitoring, but daily subcutaneous administration may reduce patients’ compliance.

VKA are usually used for long-term anticoagulation. They have the advantage of oral administration and reversibility with vitamin K supplementation, but they require international normalized ratio (INR) monitoring and a personalized dose schedule.

Beside traditional anticoagulants, in recent years direct oral anticoagulants (DOACs) have become the first choice of treatment in several conditions, such as stroke prophylaxis in atrial fibrillation[9] and treatment of deep vein thrombosis and pulmonary embolism[10].

DOACs have the advantage of oral administration, fixed dosing schedule, predictable anticoagulant effect, and they do not require frequent monitoring.

DOACs exert their activity by directly inhibiting factor X-activated (such as rivaroxaban, apixaban and edoxaban) or factor II-activated (such as dabigatran). Their metabolism is generally both renal and hepatic, with different percentage among single drugs. Rivaroxaban, apixaban and edoxaban are metabolized by cytochromes without forming active metabolites; dabigatran is a prodrug not metabolized by cytochromes and it is the DOAC with the higher amount of renal excretion (approximatively 80%)[11].

Despite the aforementioned considerations, at present the use of DOACs for SVT remains poorly investigated. If chosen as anticoagulation therapy, they have to be prescribed off-label as they are currently not licensed for this indication in many countries.

Nevertheless, on the thrust of the advantages demonstrated in other conditions, interest on the use of DOACs in this setting is recently emerging, and data obtained by several recent reports are encouraging[12,13].

In this review, we analyzed all the studies available in the literature concerning patients with cirrhotic and non-cirrhotic PVT and BCS treated with DOACs; case reports were systematically excluded.

**Non-cirrhotic PVT**

Causes of SVT in patients without underlying liver disease could be classified as systemic acquired risk factors for thrombosis, inherited thrombophilia and local factors. More than one risk factor is found in 10%-23% of patients[14,15].

Systemic acquired thrombophilic factors represent the cause of up to 50% of SVT[16]. The main related conditions are myeloproliferative neoplasms (mostly those related to JAK2-V617F mutation)[17,18], hormonal factors (oral contraceptive or pregnancy)[19,20], antiphospholipid antibody syndrome[21], and other systemic inflammations/infections (*e.g.* connective tissue disease, sarcoidosis, cytomegalovirus infection[22], severe acute respiratory syndrome coronavirus 2 infection[23,24], sepsis).

Inherited thrombophilic disorders could be detected in about 20% of cases[16]. The most common clotting factor alteration is factor V Leiden mutation (8% of cases), followed by G20210A prothrombin mutation and antithrombin deficiency (5% of cases each); protein S and protein C deficiency are less frequent (less than 2% and 1%, respectively)[25-27].

Local factors are involved in about 20% of cases[16]. These are represented mainly by abdominal surgery and infectious or inflammatory diseases involving abdominal organs, such as pancreatitis[28], diverticulitis, inflammatory bowel disease, abdominal vasculitis and abdominal cancers[17].

Notably, in 15%-40% of cases of SVT without cirrhosis no causative factors are identified. The treatment of the underlying disease is crucial in the management of patients, so an accurate work-up should be performed at SVT diagnosis[16].

Although not all guidelines agree on this definition, it is widely accepted that PVT can be divided in acute or chronic, based on the onset of the disease within 6 mo or beyond, respectively. The latter also includes the transformation in portal cavernoma, that is the replacement of the native portal vein with multiple tortuous collateral venous vessels that develop in response to chronic venous outflow obstruction.

In case of acute non-cirrhotic PVT, the main goal is to achieve portal recanalization and to prevent extension of the clot and sequelae such as intestinal infarction and the development of portal hypertension. Spontaneous resolution of acute PVT is rare, and early anticoagulation treatment is associated with higher rates of recanalization[29]. Therefore, full dose anticoagulation treatment should be started at diagnosis[15,29-33]. Moreover, a study showed that the risk of developing recurrent thrombotic events among subjects with non-abdominal thromboembolism and non-cirrhotic PVT is comparable[34].

Treatment should be continued for at least 3-6 mo for all patients. Similar to guideline recommendations for deep vein thrombosis occurring in typical sites, indefinite anticoagulation is recommended in all cases of persistent identified risk factors, such as acquired or congenital thrombophilia, but should also be considered in case the evidence of a persistent underlying prothrombotic factor is lacking[30,35].

As mentioned above, PVT may evolve into portal cavernoma if left untreated. In the presence of chronic PVT or portal cavernoma, even though the benefit of anticoagulation is less clear, it is recommended to treat patients as in the case of acute PVT[36-38]. However, since bleeding is the most common complication of chronic PVT[39], in patients with high risk esophageal varices anticoagulation treatment should be postponed until an adequate prophylaxis for portal hypertensive bleeding has been initiated[35].

Regarding the choice of anticoagulants, initial treatment with LMWH and subsequent switch to VKA is supported by extensive evidence and still represents the established therapy for most patients. The treatment is administered with the same therapeutic regimens and dose adjustments as for typical site venous thromboembolism.

Several studies have been recently published regarding the use of DOACs in this setting showing their efficacy and safety; at present, no randomized controlled trial has been published yet (Table 1).

Janczak *et al*[40] were the first to investigate the use of DOACs for thrombosis in atypical sites. They conducted a prospective study enrolling patients that were treated with anticoagulants for thromboembolism occurring both in typical and atypical sites. Considering the subgroup with PVT, 16 patients were treated with DOACs (rivaroxaban and apixaban), and 13 patients were treated with LMWH. The results did not reveal any statistically significant difference between DOACs and LMWH both in terms of efficacy and safety[40].

Scheiner *et al*[41] performed a retrospective study with 51 cirrhotic patients with concomitant non-malignant PVT. No anticoagulation therapy was started in 39 patients, whereas 12 patients received warfarin. Additionally, they also enrolled 10 patients treated with DOACs after traditional anticoagulation. In particular, 4 patients received edoxaban 30 or 60 mg once daily (OD), 3 apixaban 5 mg twice daily (BID), 2 rivaroxaban 10 mg OD, 1 dabigatran 100 mg BID. The mean follow-up time was 9.2 mo. In the DOAC group 70% of patients were non-cirrhotic. Regression of thrombus was observed in 20% of patients, and stability in 80%; no thrombus progression has been reported. Since cavernous transformation of the chronic PVT was already present in all patients treated with DOACs (therefore achieving recanalization could be difficult), the authors could not extrapolate data to compare the success rates of conservative or traditional therapy to DOACs. Only one bleeding episode was described in a patient in therapy with DOAC, so authors concluded that there was no statistically significant difference in bleeding events between DOAC and VKA groups[41].

Naymagon *et al*[42] published several retrospective studies comparing traditional anticoagulants *vs* DOACs for treatment of SVT in non-cirrhotic patients. In a study that compared VKA/LMWH and DOACs for non-cirrhotic PVT, recanalization rates (defined as complete radiological resolution) were higher in DOAC group compared to VKA, but similar to the group treated with enoxaparin. Nevertheless, a lower rate of bleeding was observed in patients treated with DOACs[42].

Another retrospective study from the same authors evaluated a cohort of 58 patients with inflammatory bowel disease associated-PVT who were treated either with DOACs or traditional anticoagulants. Complete radiological response rate in the DOAC group was two-fold higher than in the warfarin group; moreover, the DOAC group needed a shorter course of anticoagulation to achieve recanalization[43].

Similar results in terms of vein recanalization have been shown in patients who developed PVT within three months after abdominal surgery. The first group was treated with DOACs, the second with conventional anticoagulants or no anticoagulation. Recanalization rate was higher with DOAC than with VKA (77% *vs* 45%), but similar to LMWH. Of note, in the group receiving no anticoagulation treatment, only 17% of patients recanalized spontaneously[44].

Ilcewicz *et al*[45] analyzed retrospectively a cohort of 33 patients with PVT, including 10 patients with cirrhosis. Patients were treated with either warfarin or DOACs; 4 treatment failure and one major bleeding were recorded in the warfarin group but none was recorded in the DOAC group[45].

Recently, Ageno *et al*[46] conducted the first interventional study evaluating the safety and efficacy of DOACs in non-cirrhotic PVT. The study was a single-arm prospective multicentric study enrolling patients presenting with a first episode of non-cirrhotic, symptomatic, objectively diagnosed SVT who were treated with rivaroxaban 15 mg BID for 3 wk followed by 3 mo of rivaroxaban 20 mg OD. Major bleeding was the primary endpoint of the study; secondary endpoints included death, recurrent SVT, and complete vein recanalization within 3 mo. During the 6-months follow-up period, non-life-threatening major bleeding events occurred in 2 patients; recurrence of thrombosis was observed in 2 patients, and 1 death unrelated to thrombosis was recorded. The recanalization at 3 mo was achieved in more than 80% of patients, with a complete recanalization rate of 47%[46].

From what has emerged from the aforementioned studies, the use of DOACs in non-cirrhotic PVT seems to be promising; results suggest that DOACs are superior to traditional anticoagulants in terms of recanalization rate[42-44,46] although they have a similar safety profile to VKA[40].

However, it is important to emphasize that these results are affected by several limitations: Firstly, at present no randomized controlled trial has been published; secondly, the results are based on small patients cohorts, the therapeutic regimens of DOACs vary widely between studies and the duration of follow-up was also extremely heterogeneous.

**Cirrhotic PVT**

Liver cirrhosis is an irreversible end-stage liver disease characterized by the progressive deposition of fibrotic tissue and a diffuse conversion of the normal liver architecture into structurally abnormal nodules, eventually leading to impaired liver function.

The increased liver stiffness causes a reduced portal blood flow and an increase of portal pressure, (*i.e.*, portal hypertension); the blood stasis together with the pro-thrombotic status typical of cirrhotic patients lead to a higher cumulative risk of splanchnic thrombosis, mainly PVT[47,48].

A recent meta-analysis on cirrhotic PVT not treated with anticoagulation showed an improvement in 30% of cases and a progression of thrombus in approximately 25% of cases[49].

According to the Baveno VII consensus, anticoagulation is recommended in cirrhotic patients with recent (< 6 mo) and > 50% occlusive thrombosis of the main portal vein trunk, in those with symptomatic PVT or in potential candidates for liver transplantation. In the last group of patients, the aim of anticoagulation is the prevention of recurrence of thrombosis or the progression of thrombus in order to with the aim facilitate the portal anastomosis during the surgical procedure.

Anticoagulation should also be considered in patients with < 50% occlusive thrombosis of the main portal vein trunk with progression during follow-up or with extension to the superior mesenteric vein.

Once anticoagulation is started, it should be maintained until portal vein recanalization and for a minimum of 6 mo; longer anticoagulation therapy should always be considered in patients awaiting liver transplantation, even after complete portal vein recanalization[35].

Early initiation of anticoagulation seems to be related to a higher recanalization rate[50,51].

Different classifications, indications and duration of treatment, and anticoagulation of choice according to the main clinical practice guidelines[30,35,38,52] are resumed in Table 2; a deep analysis of the differences among guidelines is not the aim of this paper, so it will not be discussed further.

The assessment of the bleeding risk in cirrhotic patients is mandatory but it is always challenging. Profound alteration in coagulation pathways, related to a reduced synthesis of prothrombotic and antithrombotic clotting factors, as well as thrombocytopenia, related to hypersplenism and decreased hepatic thrombopoietin synthesis, define a hemostatic imbalance and, consequently, the management of anticoagulation therapy in cirrhotic patient could be very difficult in clinical practice[53-55].

However, anticoagulation therapy in cirrhotic patients seems to be quite safe, as demonstrated in a meta-analysis of Loffredo *et al*[56] reporting no difference in major and minor bleeding rates between patients with or without anticoagulation therapy for PVT. Moreover, a recent competing-risk meta-analysis showed that anticoagulation in patients with cirrhosis and PVT reduces all-cause mortality independently of portal recanalization[57].

The presence of hepatocellular carcinoma does not contraindicate anticoagulation for non-malignant PVT; safety and efficacy of anticoagulation seem to be similar to patients without hepatocellular carcinoma[58,59].

The choice of the best anticoagulation is still debated, and guidelines do not give strong recommendations on this topic. LMWH is the best-known treatment option, largely used and with the most solid data in the literature; for these reasons consensus panels suggest at least to start anticoagulation with this drug class[35]. Fondaparinux may be another option, although there are no significant data in the literature, especially on safety[60,61]. VKA are potentially usable[62], but physicians have to be aware that INR accuracy for treatment monitoring is significantly lower in patients with liver dysfunction[63].

Over the last few years, the clinical experience in using DOACs in patients with liver cirrhosis has been growing[64].

Despite cirrhotic patients have been excluded from phase III trials of DOACs for atrial fibrillation[65-68] and venous thromboembolism[69-72], several studies on their use in this cohort of patients have been published, demonstrating DOACs safety in patients with compensated liver disease (Child-Pugh A)[73-77]. DOACs should be used with caution in Child-Pugh B patients[78,79] and they are contraindicated in Child-Pugh C patients[80,81].

Moreover, further pharmacokinetics considerations should be considered in DOACs prescription in patients with underlying liver disease, such as altered plasma protein binding, cytochrome P450-mediated metabolism and biliary excretion[53].

Another issue is the possible hepatotoxicity of DOACs. All four available DOACs can induce hepatotoxicity with an idiosyncratic mechanism; rivaroxaban seems to have a minimally higher risk of liver injury compared to other three molecules[82]. However, recent studies have definitively shown that liver injury is a very rare adverse event and, more importantly, this rate is significantly lower than with warfarin[83-85].

Recently, several studies have been published investigating the efficacy and safety of DOAC in patients with liver cirrhosis and PVT (Table 3); In 2019, Hanafy *et al*[86] published a randomized controlled trial on rivaroxaban 10 mg BID *vs* warfarin, but it has been recently retracted for methodological issues, therefore it will not be considered in our review.

First data were obtained by Hum *et al*[87] in a single-centre retrospective cohort study of cirrhotic patients treated with anticoagulants for any indications. In the small subgroup of patients with PVT (7 patients), 4 received DOACs (rivaroxaban or apixaban) and 3 received LMWH or VKA. Of particular note, the total number of bleeding events was similar in both groups even if results are given for the entire population of study[87].

As already mentioned above, Scheiner *et al*[41] investigated a cohort of both cirrhotic and non-cirrhotic patients presenting with non-neoplastic PVT. Out of the 10 patients receiving DOACs, only 30% presented concomitant liver disease[41]. For more details about this study, refer to the previous paragraph on non-cirrhotic PVT.

De Gottardi *et al*[88] retrospectively analyzed data from 17 European centers on cirrhotic and non-cirrhotic patients all treated with DOACs (either rivaroxaban, apixaban, or dabigatran at different doses) for any indication, mainly PVT. Patients were either initially prescribed with DOACs or switched to DOACs after traditional anticoagulants. The main reasons for switching were the development of recurrent thrombosis, clinically relevant side effects, and INR instability or unreliability for monitoring cirrhotic patients. Among the entire population of 94 patients, there were 22 and 38 patients with cirrhotic and non-cirrhotic PVT, respectively. The median follow-up time was 9.6 mo. In the group of non-cirrhotic patients, bleeding event rate was 15.5% *vs* 13.9% in the cirrhotic group, suggesting that the safety of DOACs is comparable between two groups. Despite the majority of the patients presented a PVT, the results presented by the authors are referred to the entire population and actual conclusions on PVT patients alone cannot be extrapolated.

Another study examining DOACs safety in cirrhosis, but this time in comparison with conventional anticoagulants, was conducted by Intagliata *et al*[89]. After collecting data from a research database, a cohort of 39 cirrhotic patients treated with anticoagulants for various indications was identified. Since no patients with decompensated liver disease (Child-Pugh C) were treated with DOACs, only patients with Child-Pugh A or B cirrhosis were included. In the group treated with DOACs (apixaban or rivaroxaban, either in therapeutic or prophylactic doses) 20 patients were included, and the most common indication for treatment was PVT (60%). In contrast, most patients treated with VKA or LMWH presented non-splanchnic venous thromboembolism (63%). No statistically significant difference in bleeding rates was observed between the two groups.

Also Davis *et al*[90] investigated the safety of cirrhotic patients treated with DOACs or VKA for any indication. Since only 3 patients received DOAC for PVT, this study was not included in our review.

Nagaoki *et al*[91] conducted a retrospective cohort study to evaluate the efficacy of edoxaban as maintenance therapy in 50 cirrhotic patients with PVT. Child–Pugh classification was grade A in 29 patients, B in 16, and C in 5. All patients were initially treated with danaparoid sodium for two weeks and then switched to either warfarin or edoxaban 60 or 30 mg OD, depending on renal function (creatinine clearance < 30 mL/min), body weight (< 60 kg) and concomitant treatment with a strong P-glycoprotein inhibitor. Among study population, 17 patients had concomitant hepatocellular carcinoma, but all were diagnosed with non-neoplastic PVT. All patients were screened with endoscopy before the initiation of anticoagulation. In case of high risk esophageal and/or gastric varices, endoscopic prophylactic treatment was systematically performed. Median time from PVT to treatment was similar between edoxaban and VKA group (4.2 *vs* 4.3 mo, respectively). Complete recanalization, assessed by computed tomography (CT) scan at 6 mo, was observed in 14 of 20 patients (70%) in the edoxaban group and in 6 of 30 patients (20%) in the warfarin group. However, given the potential risk of bleeding, a target INR of 1.5–2.0 was chosen for patients undergoing warfarin treatment. This underdosing in VKA therapy, may explain the low efficacy rate in this cohort. Additionally, safety was considered comparable between edoxaban and warfarin groups with 3 and 2 gastrointestinal bleedings, respectively[91].

In a prospective cohort study performed by Ai *et al*[92] 80 patients with cirrhosis and chronic PVT were examined. Patients with history of recent bleeding (< 3 mo), high risk esophageal varices, systemic malignancies, severe renal impairment (creatinine clearance < 30 mL/min), concomitant antiplatelet therapy and low platelet count (< 50 × 109/L) were excluded. Of the 40 patients treated with DOACs, 26 Child-Pugh A patients were treated with rivaroxaban 20 mg OD and 14 Child-Pugh grade B or C patients with dabigatran 150 mg BID. The other 40 patients received no anticoagulation. Recanalization rates and improvements in portal vein flow velocity were analyzed at 3 and 6 mo. The recanalization rate was higher in the DOAC group than in the control group, especially after 6 mo of treatment (12.8% at 3 mo *vs* 28.2% at 6 mo), whereas the bleeding rate was similar between the 2 groups. Of note, authors considered PVT as chronic if lasting more than one month, commensurate to definition of chronic deep vein thrombosis. Overall recanalization rates were low compared to previous studies; authors suggested that the delayed initiation of anticoagulation therapy might be associated with a worse outcome[92].

Finally, Lv *et al*[93] designed a prospective observational study investigating the role of both anticoagulation and transjugular intrahepatic porto-systemic shunt (TIPS) in 396 cirrhotic patients with non-malignant PVT either acute or chronic, confirmed with CT scan. Patients with intra or extrahepatic malignancy at baseline, presence of previous TIPS, isolated mesenteric or splenic vein thrombosis, and liver transplantation recipients were excluded. Forty-eight patients received no treatment, 63 patients were treated with anticoagulants only, 88 patients received TIPS only, and 197 started anticoagulation after TIPS insertion. When patients received anticoagulation, they were treated with either VKA, LMWH, or rivaroxaban 10 mg OD, and anticoagulation treatment was extended for 12 mo after complete recanalization was achieved. A combined strategy with TIPS and subsequent anticoagulation showed the highest complete recanalization rate (188/197 patients); long-term anticoagulation with LMWH or rivaroxaban resulted in minor incidence of re-thrombosis and longer survival compared with VKA[93].

Overall, the proposed studies show that DOACs are at least non-inferior to conventional anticoagulants in cirrhotic non-malignant PVT, both in terms of efficacy and safety, but several limitations pose some issues regarding the results obtained.

First, most studies were conducted retrospectively with a limited number of patients and very heterogeneous cohorts.

Second, PVT classification, definition of bleeding events, drug dosage, and treatment duration vary widely among studies, making it difficult to compare results and to identify a standardized treatment algorithm.

Nonetheless, DOACs may represent a viable alternative to conventional anticoagulants in cirrhotic PVT, but further evidence and RCTs are needed.

**BCS**

Causes of primary BCS are essentially the same of non-cirrhotic PVT[16]. Compared with PVT, there is a greater prevalence of association with myeloproliferative neoplasm (30%-57% of cases)[17,94]. Some acquired thrombophilic conditions, such as paroxysmal nocturnal hemoglobinuria and Behçet’s disease have also a higher causative link in BCS compared with PVT (12% *vs* < 1%, respectively)[95-97]. To the contrary, BCS caused by local factors is rare, with the only exception of hepatic hydatid cysts in countries where *Echinococcus granulosus* is endemic[98].

As for PVT, more than one risk factor could be found in 26%-46% of patients and no causative factors are identified in 10%-29% of patients[16,99].

Prompt identification and treatment of an underlying disease is mandatory for the management of BCS patients since both are positively related with outcome[96,100]. Anticoagulation is the cornerstone of BCS treatment and it should be initiated at diagnosis; long-term anticoagulation is generally recommended even in the absence of an identified prothrombotic disorder[35]. LMWH is currently the drug of choice, based on several previous studies reporting a higher rate of heparin-induced thrombocytopenia in BCS patients treated with UFH[101,102]. When a stability of the disease is achieved, a switch to VKA is usually the preferred choice in clinical practice.

The role of DOACs in BCS patients has been poorly investigated compared to PVT patients.

First data came from the aforementioned retrospective study of De Gottardi *et al*[88] about the use of DOACs in both cirrhotic and non-cirrhotic patients with SVT. In the study population (94 patients) there were 9 patients with BCS treated with DOACs (dabigatran, rivaroxaban or apixaban), but as results are presented for the entire population, it is not possible to extrapolate conclusions about efficacy and safety in this cohort of patients[88].

A recent multicentric Austrian study aimed to analyze the outcome of 22 patients treated with DOACs (all four drugs were prescribed, but almost a half of patients received edoxaban) *vs* 19 patients treated with only traditional anticoagulation (*i.e.* LMWH/VKA). Authors reported better efficacy results in the DOAC cohort (64% of complete recanalization rate and 92% of overall transplant-free survival at 5 years) and a comparable risk of major spontaneous and major procedure-related bleedings. Even though the results presented are interesting, there are some general considerations about the heterogeneity of the study population to be highlighted[103].

Firstly, in the DOAC cohort 16 patients (72.7%) were already anticoagulated with traditional drugs; among these, 8 patients (50%) had already achieved a complete response at the time of switching to DOAC.

Secondly, among the 16 patients receiving DOACs it is not known the time from LMWH/VKA start to the switch to DOACs, so it is difficult to evaluate the actual efficacy or failure of DOACs in patients previously treated with traditional anticoagulation.

Lastly, the rate of objective response to the first-line anticoagulation therapy (6 patients with DOACs *vs* 37 patients with LMWH/VKA) was comparable (66.6% *vs* 67.5%, respectively)[103].

Another retrospective monocentric study, made by Sharma *et al*[104], has investigated the role of dabigatran (36 patients) following endovascular intervention for BCS compared to VKA (62 patients). Authors concluded that stent patency rate, mortality and bleeding complication rate were comparable between dabigatran and VKA groups at 6 and 12 mo[104].

Although results from the literature are limited, DOACs seem effective and safe in patients with BCS and international guidelines have consequently added these drugs as an option of treatment, but prospective studies are needed.

**CONCLUSION**

In the last few years, several studies have shown promising results in the use of DOACs for the treatment of SVT in term of efficacy and, above all, safety. Unfortunately, the majority of studies are retrospective, with small sample size and with extremely heterogeneous examined populations, not allowing to give strong recommendations about the use of DOACs in this setting. Moreover, there is no conformity among studies in dosage schedule, time of initiation and duration of treatment and bleeding event definition. In some cases, it is even not specified the DOAC used.

On the other hand, international guidelines have added this new class of drugs as an option of treatment, recognizing their potential role both in cirrhotic and non-cirrhotic patients with SVT. Although in some countries there are strict limitations in prescription, more and more physicians prescribe DOACs for SVT in their clinical practice worldwide.

Further studies and clinical trials are needed in order to increase the level of evidence in this field, but current knowledge on DOAC use is already changing the therapeutic scenario of SVT.

**REFERENCES**

1 **Di Nisio M**, Valeriani E, Riva N, Schulman S, Beyer-Westendorf J, Ageno W. Anticoagulant therapy for splanchnic vein thrombosis: ISTH SSC Subcommittee Control of Anticoagulation. *J Thromb Haemost* 2020; **18**: 1562-1568 [PMID: 32619346 DOI: 10.1111/jth.14836]

2 **Jones DEJ**, Sturm E, Lohse AW. Access to care in rare liver diseases: New challenges and new opportunities. *J Hepatol* 2018; **68**: 577-585 [PMID: 29113911 DOI: 10.1016/j.jhep.2017.11.004]

3 **Francoz C**, Valla D, Durand F. Portal vein thrombosis, cirrhosis, and liver transplantation. *J Hepatol* 2012; **57**: 203-212 [PMID: 22446690 DOI: 10.1016/j.jhep.2011.12.034]

4 **Nery F**, Chevret S, Condat B, de Raucourt E, Boudaoud L, Rautou PE, Plessier A, Roulot D, Chaffaut C, Bourcier V, Trinchet JC, Valla DC; Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire. Causes and consequences of portal vein thrombosis in 1,243 patients with cirrhosis: results of a longitudinal study. *Hepatology* 2015; **61**: 660-667 [PMID: 25284616 DOI: 10.1002/hep.27546]

5 **Senzolo M**, Garcia-Tsao G, García-Pagán JC. Current knowledge and management of portal vein thrombosis in cirrhosis. *J Hepatol* 2021; **75**: 442-453 [PMID: 33930474 DOI: 10.1016/j.jhep.2021.04.029]

6 **Cheng Q**, Tree K. Systematic Review of Thrombolysis Therapy in the Management of Non-Cirrhosis-Related Portal Vein Thrombosis. *J Gastrointest Surg* 2021; **25**: 1579-1590 [PMID: 33452971 DOI: 10.1007/s11605-020-04624-4]

7 **Gadani S**, Partovi S, Levitin A, Zerona N, Sengupta S, D'Amico G, Diago Uso T, Menon KVN, Quintini C. Narrative review of portal vein thrombosis in cirrhosis: pathophysiology, diagnosis, and management from an interventional radiology perspective. *Cardiovasc Diagn Ther* 2022; **12**: 135-146 [PMID: 35282661 DOI: 10.21037/cdt-21-98]

8 **Saito H**, Sugihara F, Ueda T, Hayashi H, Shirai S, Matsumoto T, Fujitsuna R, Kumita SI. Efficacy of endovascular treatment for completely occlusive acute-subacute portal and mesenteric vein thrombosis with severe complications in patients without cirrhosis. *Jpn J Radiol* 2023; **41**: 541-550 [PMID: 36680703 DOI: 10.1007/s11604-022-01377-9]

9 **Steffel J**, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG, Oldgren J, Reinecke H, Roldan-Schilling V, Rowell N, Sinnaeve P, Vanassche T, Potpara T, Camm AJ, Heidbüchel H; External reviewers. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. *Europace* 2021; **23**: 1612-1676 [PMID: 33895845 DOI: 10.1093/europace/euab065]

10 **Konstantinides SV**, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, Huisman MV, Humbert M, Jennings CS, Jiménez D, Kucher N, Lang IM, Lankeit M, Lorusso R, Mazzolai L, Meneveau N, Ní Áinle F, Prandoni P, Pruszczyk P, Righini M, Torbicki A, Van Belle E, Zamorano JL; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J* 2020; **41**: 543-603 [PMID: 31504429 DOI: 10.1093/eurheartj/ehz405]

11 **Harder S**, Graff J. Novel oral anticoagulants: clinical pharmacology, indications and practical considerations. *Eur J Clin Pharmacol* 2013; **69**: 1617-1633 [PMID: 23619611 DOI: 10.1007/s00228-013-1510-z]

12 **Gupta S**, Hidalgo J, Singh B, Iyer A, Yang Y, Short A, Singh S, Bhatt H, Gupta S. Usage of Direct Acting Oral Anticoagulants in Cirrhotic and Non-Cirrhotic Portal Vein Thrombosis: A Systematic Review. *Cureus* 2021; **13**: e16922 [PMID: 34367844 DOI: 10.7759/cureus.16922]

13 **Biolato M**, Paratore M, Di Gialleonardo L, Marrone G, Grieco A. Direct oral anticoagulant administration in cirrhotic patients with portal vein thrombosis: What is the evidence? *World J Hepatol* 2022; **14**: 682-695 [PMID: 35646264 DOI: 10.4254/wjh.v14.i4.682]

14 **Denninger MH**, Chaït Y, Casadevall N, Hillaire S, Guillin MC, Bezeaud A, Erlinger S, Briere J, Valla D. Cause of portal or hepatic venous thrombosis in adults: the role of multiple concurrent factors. *Hepatology* 2000; **31**: 587-591 [PMID: 10706547 DOI: 10.1002/hep.510310307]

15 **Plessier A**, Darwish-Murad S, Hernandez-Guerra M, Consigny Y, Fabris F, Trebicka J, Heller J, Morard I, Lasser L, Langlet P, Denninger MH, Vidaud D, Condat B, Hadengue A, Primignani M, Garcia-Pagan JC, Janssen HL, Valla D; European Network for Vascular Disorders of the Liver (EN-Vie). Acute portal vein thrombosis unrelated to cirrhosis: a prospective multicenter follow-up study. *Hepatology* 2010; **51**: 210-218 [PMID: 19821530 DOI: 10.1002/hep.23259]

16 **Elkrief L**, Payancé A, Plessier A, d'Alteroche L, Ronot M, Paradis V, Valla D, Rautou PE. Management of splanchnic vein thrombosis. *JHEP Rep* 2023; **5**: 100667 [PMID: 36941824 DOI: 10.1016/j.jhepr.2022.100667]

17 **Smalberg JH**, Arends LR, Valla DC, Kiladjian JJ, Janssen HL, Leebeek FW. Myeloproliferative neoplasms in Budd-Chiari syndrome and portal vein thrombosis: a meta-analysis. *Blood* 2012; **120**: 4921-4928 [PMID: 23043069 DOI: 10.1182/blood-2011-09-376517]

18 **Debureaux PE**, Cassinat B, Soret-Dulphy J, Mora B, Verger E, Maslah N, Plessier A, Rautou PE, Ollivier-Hourman I, De Ledinghen V, Goria O, Bureau C, Siracusa C, Valla D, Giraudier S, Passamonti F, Kiladjian JJ. Molecular profiling and risk classification of patients with myeloproliferative neoplasms and splanchnic vein thromboses. *Blood Adv* 2020; **4**: 3708-3715 [PMID: 32777065 DOI: 10.1182/bloodadvances.2020002414]

19 **Rajani R**, Björnsson E, Bergquist A, Danielsson A, Gustavsson A, Grip O, Melin T, Sangfelt P, Wallerstedt S, Almer S. The epidemiology and clinical features of portal vein thrombosis: a multicentre study. *Aliment Pharmacol Ther* 2010; **32**: 1154-1162 [PMID: 21039677 DOI: 10.1111/j.1365-2036.2010.04454.x]

20 **Bissonnette J**, Durand F, de Raucourt E, Ceccaldi PF, Plessier A, Valla D, Rautou PE. Pregnancy and vascular liver disease. *J Clin Exp Hepatol* 2015; **5**: 41-50 [PMID: 25941432 DOI: 10.1016/j.jceh.2014.12.007]

21 **Qi X**, De Stefano V, Su C, Bai M, Guo X, Fan D. Associations of antiphospholipid antibodies with splanchnic vein thrombosis: a systematic review with meta-analysis. *Medicine (Baltimore)* 2015; **94**: e496 [PMID: 25634200 DOI: 10.1097/MD.0000000000000496]

22 **De Broucker C**, Plessier A, Ollivier-Hourmand I, Dharancy S, Bureau C, Cervoni JP, Sogni P, Goria O, Corcos O, Sartoris R, Ronot M, Vilgrain V, de Raucourt E, Zekrini K, Davy H, Durand F, Payancé A, Fidouh-Houhou N, Yazdanpanah Y, Valla D, Rautou PE. Multicenter study on recent portal venous system thrombosis associated with cytomegalovirus disease. *J Hepatol* 2022; **76**: 115-122 [PMID: 34563580 DOI: 10.1016/j.jhep.2021.09.011]

23 **Buso G**, Becchetti C, Berzigotti A. Acute splanchnic vein thrombosis in patients with COVID-19: A systematic review. *Dig Liver Dis* 2021; **53**: 937-949 [PMID: 34120860 DOI: 10.1016/j.dld.2021.05.021]

24 **Baiges A**, Cerda E, Amicone C, Téllez L, Alvarado-Tapias E, Puente A, Fortea JI, Llop E, Rocha F, Orts L, Ros-Fargas O, Vizcarra P, Zekrini K, Lounes OA, Touati G, Jiménez-Esquivel N, Serrano MJ, Falgà A, Magaz M, Olivas P, Betancourt F, Perez-Campuzano V, Turon F, Payancé A, Goria O, Rautou PE, Hernández-Gea V, Villanueva C, Albillos A, Plessier A, García-Pagán JC. Impact of SARS-CoV-2 Pandemic on Vascular Liver Diseases. *Clin Gastroenterol Hepatol* 2022; **20**: 1525-1533.e5 [PMID: 34968728 DOI: 10.1016/j.cgh.2021.12.032]

25 **Qi X**, Ren W, De Stefano V, Fan D. Associations of coagulation factor V Leiden and prothrombin G20210A mutations with Budd-Chiari syndrome and portal vein thrombosis: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2014; **12**: 1801-12.e7 [PMID: 24793031 DOI: 10.1016/j.cgh.2014.04.026]

26 **Poisson J**, Plessier A, Kiladjian JJ, Turon F, Cassinat B, Andreoli A, De Raucourt E, Goria O, Zekrini K, Bureau C, Lorre F, Cervantes F, Colomer D, Durand F, Garcia-Pagan JC, Casadevall N, Valla DC, Rautou PE, Marzac C; French national network for vascular liver diseases. Selective testing for calreticulin gene mutations in patients with splanchnic vein thrombosis: A prospective cohort study. *J Hepatol* 2017; **67**: 501-507 [PMID: 28483676 DOI: 10.1016/j.jhep.2017.04.021]

27 **Baiges A**, de la Morena-Barrio ME, Turon F, Miñano A, Alberto Ferrusquía J, Magaz M, Reverter JC, Vicente V, Hernández-Gea V, Corral J, García-Pagán JC. Congenital antithrombin deficiency in patients with splanchnic vein thrombosis. *Liver Int* 2020; **40**: 1168-1177 [PMID: 31885188 DOI: 10.1111/liv.14342]

28 **Rebours V**, Boudaoud L, Vullierme MP, Vidaud D, Condat B, Hentic O, Maire F, Hammel P, Ruszniewski P, Lévy P. Extrahepatic portal venous system thrombosis in recurrent acute and chronic alcoholic pancreatitis is caused by local inflammation and not thrombophilia. *Am J Gastroenterol* 2012; **107**: 1579-1585 [PMID: 22825367 DOI: 10.1038/ajg.2012.231]

29 **Condat B**, Pessione F, Helene Denninger M, Hillaire S, Valla D. Recent portal or mesenteric venous thrombosis: increased recognition and frequent recanalization on anticoagulant therapy. *Hepatology* 2000; **32**: 466-470 [PMID: 10960436 DOI: 10.1053/jhep.2000.16597]

30 **European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu**. EASL Clinical Practice Guidelines: Vascular diseases of the liver. *J Hepatol* 2016; **64**: 179-202 [PMID: 26516032 DOI: 10.1016/j.jhep.2015.07.040]

31 **Amitrano L**, Guardascione MA, Scaglione M, Pezzullo L, Sangiuliano N, Armellino MF, Manguso F, Margaglione M, Ames PR, Iannaccone L, Grandone E, Romano L, Balzano A. Prognostic factors in noncirrhotic patients with splanchnic vein thromboses. *Am J Gastroenterol* 2007; **102**: 2464-2470 [PMID: 17958760 DOI: 10.1111/j.1572-0241.2007.01477.x]

32 **Hall TC**, Garcea G, Metcalfe M, Bilku D, Dennison AR. Management of acute non-cirrhotic and non-malignant portal vein thrombosis: a systematic review. *World J Surg* 2011; **35**: 2510-2520 [PMID: 21882035 DOI: 10.1007/s00268-011-1198-0]

33 **Turnes J**, García-Pagán JC, González M, Aracil C, Calleja JL, Ripoll C, Abraldes JG, Bañares R, Villanueva C, Albillos A, Ayuso JR, Gilabert R, Bosch J. Portal hypertension-related complications after acute portal vein thrombosis: impact of early anticoagulation. *Clin Gastroenterol Hepatol* 2008; **6**: 1412-1417 [PMID: 19081529 DOI: 10.1016/j.cgh.2008.07.031]

34 **Ageno W**, Riva N, Schulman S, Beyer-Westendorf J, Bang SM, Senzolo M, Grandone E, Pasca S, Di Minno MN, Duce R, Malato A, Santoro R, Poli D, Verhamme P, Martinelli I, Kamphuisen P, Oh D, D'Amico E, Becattini C, De Stefano V, Vidili G, Vaccarino A, Nardo B, Di Nisio M, Dentali F. Long-term Clinical Outcomes of Splanchnic Vein Thrombosis: Results of an International Registry. *JAMA Intern Med* 2015; **175**: 1474-1480 [PMID: 26168152 DOI: 10.1001/jamainternmed.2015.3184]

35 **de Franchis R**, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C; Baveno VII Faculty. Baveno VII - Renewing consensus in portal hypertension. *J Hepatol* 2022; **76**: 959-974 [PMID: 35120736 DOI: 10.1016/j.jhep.2021.12.022]

36 **Intagliata NM**, Saad WE, Caldwell SH. Effects of restoring portal flow with anticoagulation and partial splenorenal shunt embolization. *Hepatology* 2015; **61**: 1088-1090 [PMID: 24867875 DOI: 10.1002/hep.27241]

37 **Chen H**, Turon F, Hernández-Gea V, Fuster J, Garcia-Criado A, Barrufet M, Darnell A, Fondevila C, Garcia-Valdecasas JC, Garcia-Pagán JC. Nontumoral portal vein thrombosis in patients awaiting liver transplantation. *Liver Transpl* 2016; **22**: 352-365 [PMID: 26684272 DOI: 10.1002/lt.24387]

38 **Northup PG**, Garcia-Pagan JC, Garcia-Tsao G, Intagliata NM, Superina RA, Roberts LN, Lisman T, Valla DC. Vascular Liver Disorders, Portal Vein Thrombosis, and Procedural Bleeding in Patients With Liver Disease: 2020 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2021; **73**: 366-413 [PMID: 33219529 DOI: 10.1002/hep.31646]

39 **Spaander MC**, Hoekstra J, Hansen BE, Van Buuren HR, Leebeek FW, Janssen HL. Anticoagulant therapy in patients with non-cirrhotic portal vein thrombosis: effect on new thrombotic events and gastrointestinal bleeding. *J Thromb Haemost* 2013; **11**: 452-459 [PMID: 23289370 DOI: 10.1111/jth.12121]

40 **Janczak DT**, Mimier MK, McBane RD, Kamath PS, Simmons BS, Bott-Kitslaar DM, Lenz CJ, Vargas ER, Hodge DO, Wysokinski WE. Rivaroxaban and Apixaban for Initial Treatment of Acute Venous Thromboembolism of Atypical Location. *Mayo Clin Proc* 2018; **93**: 40-47 [PMID: 29217335 DOI: 10.1016/j.mayocp.2017.10.007]

41 **Scheiner B**, Stammet PR, Pokorny S, Bucsics T, Schwabl P, Brichta A, Thaler J, Lampichler K, Ba-Ssalamah A, Ay C, Ferlitsch A, Trauner M, Mandorfer M, Reiberger T. Anticoagulation in non-malignant portal vein thrombosis is safe and improves hepatic function. *Wien Klin Wochenschr* 2018; **130**: 446-455 [PMID: 29916054 DOI: 10.1007/s00508-018-1351-y]

42 **Naymagon L**, Tremblay D, Zubizarreta N, Moshier E, Troy K, Schiano T, Mascarenhas J. The efficacy and safety of direct oral anticoagulants in noncirrhotic portal vein thrombosis. *Blood Adv* 2020; **4**: 655-666 [PMID: 32078681 DOI: 10.1182/bloodadvances.2019001310]

43 **Naymagon L**, Tremblay D, Zubizarreta N, Moshier E, Naymagon S, Mascarenhas J, Schiano T. The Natural History, Treatments, and Outcomes of Portal Vein Thrombosis in Patients With Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2021; **27**: 215-223 [PMID: 32185400 DOI: 10.1093/ibd/izaa053]

44 **Naymagon L**, Tremblay D, Mascarenhas J, Schiano T. Characteristics, anticoagulation, and outcomes of portal vein thrombosis after intra-abdominal surgery. *Surgery* 2021; **169**: 1175-1181 [PMID: 33358635 DOI: 10.1016/j.surg.2020.11.016]

45 **Ilcewicz HN**, Martello JL, Piechowski K. Evaluation of the efficacy and safety of direct oral anticoagulants in the treatment of portal vein thrombosis. *Eur J Gastroenterol Hepatol* 2021; **33**: 911-916 [PMID: 33079786 DOI: 10.1097/MEG.0000000000001958]

46 **Ageno W**, Beyer Westendorf J, Contino L, Bucherini E, Sartori MT, Senzolo M, Grandone E, Santoro R, Carrier M, Delluc A, De Stefano V, Pomero F, Donadini MP, Tosetto A, Becattini C, Martinelli I, Nardo B, Bertoletti L, Di Nisio M, Lazo-Langner A, Schenone A, Riva N. Rivaroxaban for the treatment of noncirrhotic splanchnic vein thrombosis: an interventional prospective cohort study. *Blood Adv* 2022; **6**: 3569-3578 [PMID: 35439303 DOI: 10.1182/bloodadvances.2022007397]

47 **Intagliata NM**, Caldwell SH, Tripodi A. Diagnosis, Development, and Treatment of Portal Vein Thrombosis in Patients With and Without Cirrhosis. *Gastroenterology* 2019; **156**: 1582-1599.e1 [PMID: 30771355 DOI: 10.1053/j.gastro.2019.01.265]

48 **Prakash S**, Bies J, Hassan M, Mares A, Didia SC. Portal vein thrombosis in cirrhosis: A literature review. *Front Med (Lausanne)* 2023; **10**: 1134801 [PMID: 37181351 DOI: 10.3389/fmed.2023.1134801]

49 **Giri S**, Singh A, Kolhe K, Kale A, Shukla A. Natural history of portal vein thrombosis in cirrhosis: A systematic review with meta-analysis. *J Gastroenterol Hepatol* 2023 [PMID: 37354011 DOI: 10.1111/jgh.16263]

50 **Senzolo M**, M Sartori T, Rossetto V, Burra P, Cillo U, Boccagni P, Gasparini D, Miotto D, Simioni P, Tsochatzis E, A Burroughs K. Prospective evaluation of anticoagulation and transjugular intrahepatic portosystemic shunt for the management of portal vein thrombosis in cirrhosis. *Liver Int* 2012; **32**: 919-927 [PMID: 22435854 DOI: 10.1111/j.1478-3231.2012.02785.x]

51 **Delgado MG**, Seijo S, Yepes I, Achécar L, Catalina MV, García-Criado A, Abraldes JG, de la Peña J, Bañares R, Albillos A, Bosch J, García-Pagán JC. Efficacy and safety of anticoagulation on patients with cirrhosis and portal vein thrombosis. *Clin Gastroenterol Hepatol* 2012; **10**: 776-783 [PMID: 22289875 DOI: 10.1016/j.cgh.2012.01.012]

52 **Simonetto DA**, Singal AK, Garcia-Tsao G, Caldwell SH, Ahn J, Kamath PS. ACG Clinical Guideline: Disorders of the Hepatic and Mesenteric Circulation. *Am J Gastroenterol* 2020; **115**: 18-40 [PMID: 31895720 DOI: 10.14309/ajg.0000000000000486]

53 **Turco L**, de Raucourt E, Valla DC, Villa E. Anticoagulation in the cirrhotic patient. *JHEP Rep* 2019; **1**: 227-239 [PMID: 32039373 DOI: 10.1016/j.jhepr.2019.02.006]

54 **Lisman T**, Caldwell SH, Intagliata NM. Haemostatic alterations and management of haemostasis in patients with cirrhosis. *J Hepatol* 2022; **76**: 1291-1305 [PMID: 35589251 DOI: 10.1016/j.jhep.2021.11.004]

55 **Rautou PE**, Caldwell SH, Villa E. Bleeding and Thrombotic Complications in Patients With Cirrhosis: A State-of-the-Art Appraisal. *Clin Gastroenterol Hepatol* 2023; **21**: 2110-2123 [PMID: 37121529 DOI: 10.1016/j.cgh.2023.04.016]

56 **Loffredo L**, Pastori D, Farcomeni A, Violi F. Effects of Anticoagulants in Patients With Cirrhosis and Portal Vein Thrombosis: A Systematic Review and Meta-analysis. *Gastroenterology* 2017; **153**: 480-487.e1 [PMID: 28479379 DOI: 10.1053/j.gastro.2017.04.042]

57 **Guerrero A**, Campo LD, Piscaglia F, Scheiner B, Han G, Violi F, Ferreira CN, Téllez L, Reiberger T, Basili S, Zamora J, Albillos A; Baveno Cooperation: an EASL consortium. Anticoagulation improves survival in patients with cirrhosis and portal vein thrombosis: The IMPORTAL competing-risk meta-analysis. *J Hepatol* 2023; **79**: 69-78 [PMID: 36858157 DOI: 10.1016/j.jhep.2023.02.023]

58 **Pettinari I**, Vukotic R, Stefanescu H, Pecorelli A, Morelli M, Grigoras C, Sparchez Z, Andreone P, Piscaglia F; BO-LIVES (BOlogna LIVEr vascular Studies). Clinical Impact and Safety of Anticoagulants for Portal Vein Thrombosis in Cirrhosis. *Am J Gastroenterol* 2019; **114**: 258-266 [PMID: 30538290 DOI: 10.1038/s41395-018-0421-0]

59 **Benevento F**, Pecorelli A, Stefanescu H, Sparchez Z, Vukotic R, Pettinari I, Grigoras CA, Tovoli F, Ravaioli F, Stefanini B, Andreone P, Piscaglia F. Presence of Hepatocellular Carcinoma Does Not Affect Course and Response to Anticoagulation of Bland Portal Vein Thrombosis in Cirrhotic Patients. *J Hepatocell Carcinoma* 2023; **10**: 473-482 [PMID: 37007210 DOI: 10.2147/JHC.S390777]

60 **Zhang ZH**, Zhang JW, He P, Zhou Y, Sun CY. Fondaparinux is effective for acute portal vein thrombosis in decompensated cirrhotic patients. *Medicine (Baltimore)* 2017; **96**: e8256 [PMID: 29049216 DOI: 10.1097/MD.0000000000008256]

61 **Senzolo M**, Piano S, Shalaby S, Tonon M, Tonello S, Zanetto A, Sacerdoti D, Simioni P, Bombonato G, Burra P, Angeli P. Comparison of Fondaparinux and Low-Molecular-Weight Heparin in the Treatment of Portal Vein Thrombosis in Cirrhosis. *Am J Med* 2021; **134**: 1278-1285.e2 [PMID: 34197784 DOI: 10.1016/j.amjmed.2021.05.013]

62 **Zhou T**, Sun X, Zhou T, Li Y, Chen X, Cheng B, Gao Y. Efficacy and Safety of Nadroparin Calcium-Warfarin Sequential Anticoagulation in Portal Vein Thrombosis in Cirrhotic Patients: A Randomized Controlled Trial. *Clin Transl Gastroenterol* 2020; **11**: e00228 [PMID: 32858573 DOI: 10.14309/ctg.0000000000000228]

63 **Tripodi A**, Fracanzani AL, Primignani M, Chantarangkul V, Clerici M, Mannucci PM, Peyvandi F, Bertelli C, Valenti L, Fargion S. Procoagulant imbalance in patients with non-alcoholic fatty liver disease. *J Hepatol* 2014; **61**: 148-154 [PMID: 24657400 DOI: 10.1016/j.jhep.2014.03.013]

64 **Koh JH**, Liew ZH, Ng GK, Liu HT, Tam YC, De Gottardi A, Wong YJ. Efficacy and safety of direct oral anticoagulants *vs* vitamin K antagonist for portal vein thrombosis in cirrhosis: A systematic review and meta-analysis. *Dig Liver Dis* 2022; **54**: 56-62 [PMID: 34393072 DOI: 10.1016/j.dld.2021.07.039]

65 **Connolly SJ**, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran *vs* warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; **361**: 1139-1151 [PMID: 19717844 DOI: 10.1056/NEJMoa0905561]

66 **Patel MR**, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban *vs* warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; **365**: 883-891 [PMID: 21830957 DOI: 10.1056/NEJMoa1009638]

67 **Granger CB**, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L; ARISTOTLE Committees and Investigators. Apixaban *vs* warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; **365**: 981-992 [PMID: 21870978 DOI: 10.1056/NEJMoa1107039]

68 **Giugliano RP**, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM; ENGAGE AF-TIMI 48 Investigators. Edoxaban *vs* warfarin in patients with atrial fibrillation. *N Engl J Med* 2013; **369**: 2093-2104 [PMID: 24251359 DOI: 10.1056/NEJMoa1310907]

69 **Schulman S**, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, Baanstra D, Schnee J, Goldhaber SZ; RE-COVER Study Group. Dabigatran *vs* warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009; **361**: 2342-2352 [PMID: 19966341 DOI: 10.1056/NEJMoa0906598]

70 **EINSTEIN Investigators**, Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, Lensing AW, Misselwitz F, Prins MH, Raskob GE, Segers A, Verhamme P, Wells P, Agnelli G, Bounameaux H, Cohen A, Davidson BL, Piovella F, Schellong S. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010; **363**: 2499-2510 [PMID: 21128814 DOI: 10.1056/NEJMoa1007903]

71 **Agnelli G**, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, Weitz JI; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013; **369**: 799-808 [PMID: 23808982 DOI: 10.1056/NEJMoa1302507]

72 **Hokusai-VTE Investigators**, Büller HR, Décousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH, Raskob GE, Schellong SM, Schwocho L, Segers A, Shi M, Verhamme P, Wells P. Edoxaban *vs* warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013; **369**: 1406-1415 [PMID: 23991658 DOI: 10.1056/NEJMoa1306638]

73 **Hoolwerf EW**, Kraaijpoel N, Büller HR, van Es N. Direct oral anticoagulants in patients with liver cirrhosis: A systematic review. *Thromb Res* 2018; **170**: 102-108 [PMID: 30153564 DOI: 10.1016/j.thromres.2018.08.011]

74 **Menichelli D**, Ronca V, Di Rocco A, Pignatelli P, Marco Podda G; CAR. Direct oral anticoagulants and advanced liver disease: A systematic review and meta-analysis. *Eur J Clin Invest* 2021; **51**: e13397 [PMID: 32895926 DOI: 10.1111/eci.13397]

75 **Serper M**, Weinberg EM, Cohen JB, Reese PP, Taddei TH, Kaplan DE. Mortality and Hepatic Decompensation in Patients With Cirrhosis and Atrial Fibrillation Treated With Anticoagulation. *Hepatology* 2021; **73**: 219-232 [PMID: 32267547 DOI: 10.1002/hep.31264]

76 **Yoo SY**, Kim E, Nam GB, Lee D, Shim JH, Kim KM, Lim YS, Lee HC, Chung YH, Lee YS, Choi J. Safety of direct oral anticoagulants compared to warfarin in cirrhotic patients with atrial fibrillation. *Korean J Intern Med* 2022; **37**: 555-566 [PMID: 35078306 DOI: 10.3904/kjim.2020.622]

77 **Li Z**, Xu W, Wang L, Chai L, Ageno W, Romeiro FG, Li H, Qi X. Risk of Bleeding in Liver Cirrhosis Receiving Direct Oral Anticoagulants: A Systematic Review and Meta-analysis. *Thromb Haemost* 2023 [PMID: 37336474 DOI: 10.1055/s-0043-1770100]

78 **Kubitza D**, Roth A, Becka M, Alatrach A, Halabi A, Hinrichsen H, Mueck W. Effect of hepatic impairment on the pharmacokinetics and pharmacodynamics of a single dose of rivaroxaban, an oral, direct Factor Xa inhibitor. *Br J Clin Pharmacol* 2013; **76**: 89-98 [PMID: 23294275 DOI: 10.1111/bcp.12054]

79 **Violi F**, Loffredo L, Pastori D. Anticoagulation in patients with advanced liver disease: an open issue. *Intern Emerg Med* 2021; **16**: 61-71 [PMID: 33073317 DOI: 10.1007/s11739-020-02526-6]

80 **Mort JF**, Davis JPE, Mahoro G, Stotts MJ, Intagliata NM, Northup PG. Rates of Bleeding and Discontinuation of Direct Oral Anticoagulants in Patients With Decompensated Cirrhosis. *Clin Gastroenterol Hepatol* 2021; **19**: 1436-1442 [PMID: 32777555 DOI: 10.1016/j.cgh.2020.08.007]

81 **Semmler G**, Pomej K, Bauer DJM, Balcar L, Simbrunner B, Binter T, Hartl L, Becker J, Pinter M, Quehenberger P, Trauner M, Mandorfer M, Lisman T, Reiberger T, Scheiner B. Safety of direct oral anticoagulants in patients with advanced liver disease. *Liver Int* 2021; **41**: 2159-2170 [PMID: 34152697 DOI: 10.1111/liv.14992]

82 **Licata A**, Puccia F, Lombardo V, Serruto A, Minissale MG, Morreale I, Giannitrapani L, Soresi M, Montalto G, Almasio PL. Rivaroxaban-induced hepatotoxicity: review of the literature and report of new cases. *Eur J Gastroenterol Hepatol* 2018; **30**: 226-232 [PMID: 29120909 DOI: 10.1097/MEG.0000000000001030]

83 **Liakoni E**, Rätz Bravo AE, Krähenbühl S. Hepatotoxicity of New Oral Anticoagulants (NOACs). *Drug Saf* 2015; **38**: 711-720 [PMID: 26138527 DOI: 10.1007/s40264-015-0317-5]

84 **Caldeira D**, Barra M, Santos AT, de Abreu D, Pinto FJ, Ferreira JJ, Costa J. Risk of drug-induced liver injury with the new oral anticoagulants: systematic review and meta-analysis. *Heart* 2014; **100**: 550-556 [PMID: 24476812 DOI: 10.1136/heartjnl-2013-305288]

85 **Alonso A**, MacLehose RF, Chen LY, Bengtson LG, Chamberlain AM, Norby FL, Lutsey PL. Prospective study of oral anticoagulants and risk of liver injury in patients with atrial fibrillation. *Heart* 2017; **103**: 834-839 [PMID: 28057799 DOI: 10.1136/heartjnl-2016-310586]

86 **Hanafy AS**, Abd-Elsalam S, Dawoud MM. Randomized controlled trial of rivaroxaban *vs* warfarin in the management of acute non-neoplastic portal vein thrombosis. *Vascul Pharmacol* 2019; **113**: 86-91 [PMID: 29886103 DOI: 10.1016/j.vph.2018.05.002]

87 **Hum J**, Shatzel JJ, Jou JH, Deloughery TG. The efficacy and safety of direct oral anticoagulants *vs* traditional anticoagulants in cirrhosis. *Eur J Haematol* 2017; **98**: 393-397 [PMID: 28009449 DOI: 10.1111/ejh.12844]

88 **De Gottardi A**, Trebicka J, Klinger C, Plessier A, Seijo S, Terziroli B, Magenta L, Semela D, Buscarini E, Langlet P, Görtzen J, Puente A, Müllhaupt B, Navascuès C, Nery F, Deltenre P, Turon F, Engelmann C, Arya R, Caca K, Peck-Radosavljevic M, Leebeek FWG, Valla D, Garcia-Pagan JC; VALDIG Investigators. Antithrombotic treatment with direct-acting oral anticoagulants in patients with splanchnic vein thrombosis and cirrhosis. *Liver Int* 2017; **37**: 694-699 [PMID: 27778440 DOI: 10.1111/liv.13285]

89 **Intagliata NM**, Henry ZH, Maitland H, Shah NL, Argo CK, Northup PG, Caldwell SH. Direct Oral Anticoagulants in Cirrhosis Patients Pose Similar Risks of Bleeding When Compared to Traditional Anticoagulation. *Dig Dis Sci* 2016; **61**: 1721-1727 [PMID: 26725062 DOI: 10.1007/s10620-015-4012-2]

90 **Davis KA**, Joseph J, Nisly SA. Direct oral anticoagulants and warfarin in patients with cirrhosis: a comparison of outcomes. *J Thromb Thrombolysis* 2020; **50**: 457-461 [PMID: 31915998 DOI: 10.1007/s11239-019-02035-0]

91 **Nagaoki Y**, Aikata H, Daijyo K, Teraoka Y, Shinohara F, Nakamura Y, Hatooka M, Morio K, Nakahara T, Kawaoka T, Tsuge M, Hiramatsu A, Imamura M, Kawakami Y, Ochi H, Chayama K. Efficacy and safety of edoxaban for treatment of portal vein thrombosis following danaparoid sodium in patients with liver cirrhosis. *Hepatol Res* 2018; **48**: 51-58 [PMID: 28342265 DOI: 10.1111/hepr.12895]

92 **Ai MH**, Dong WG, Tan XP, Xu L, Xu C, Zhang Q, Zhang Y, Li J. Efficacy and safety study of direct-acting oral anticoagulants for the treatment of chronic portal vein thrombosis in patients with liver cirrhosis. *Eur J Gastroenterol Hepatol* 2020; **32**: 1395-1400 [PMID: 32675774 DOI: 10.1097/MEG.0000000000001846]

93 **Lv Y**, Bai W, Li K, Wang Z, Guo W, Luo B, Wang J, Wang Q, Wang E, Xia D, Li X, Yuan J, Han N, Niu J, Yin Z, Fan D, Han G. Anticoagulation and Transjugular Intrahepatic Portosystemic Shunt for the Management of Portal Vein Thrombosis in Cirrhosis: A Prospective Observational Study. *Am J Gastroenterol* 2021; **116**: 1447-1464 [PMID: 33630766 DOI: 10.14309/ajg.0000000000001194]

94 **Qi X**, Han G, Guo X, De Stefano V, Xu K, Lu Z, Xu H, Mancuso A, Zhang W, Han X, Valla DC, Fan D. Review article: the aetiology of primary Budd-Chiari syndrome - differences between the West and China. *Aliment Pharmacol Ther* 2016; **44**: 1152-1167 [PMID: 27734511 DOI: 10.1111/apt.13815]

95 **Hoekstra J**, Leebeek FW, Plessier A, Raffa S, Darwish Murad S, Heller J, Hadengue A, Chagneau C, Elias E, Primignani M, Garcia-Pagan JC, Valla DC, Janssen HL; European Network for Vascular Disorders of the Liver. Paroxysmal nocturnal hemoglobinuria in Budd-Chiari syndrome: findings from a cohort study. *J Hepatol* 2009; **51**: 696-706 [PMID: 19664836 DOI: 10.1016/j.jhep.2009.06.019]

96 **Desbois AC**, Rautou PE, Biard L, Belmatoug N, Wechsler B, Resche-Rigon M, Zarrouk V, Fantin B, de Chambrun MP, Cacoub P, Valla D, Saadoun D, Plessier A. Behcet's disease in Budd-Chiari syndrome. *Orphanet J Rare Dis* 2014; **9**: 104 [PMID: 25213625 DOI: 10.1186/s13023-014-0153-1]

97 **Sakr MA**, Reda MA, Ebada HE, Abdelmoaty AS, Hefny ZM, Ibrahim ZH, Aboelmaaty ME. Characteristics and outcome of primary Budd-Chiari syndrome due to Behçet's syndrome. *Clin Res Hepatol Gastroenterol* 2020; **44**: 503-512 [PMID: 31735495 DOI: 10.1016/j.clinre.2019.10.006]

98 **Afredj N**, Guessab N, Nani A, Faraoun SA, Ouled Cheikh I, Kerbouche R, Hannoun D, Amir ZC, Ait Kaci H, Bentabak K, Plessier A, Valla DC, Cazals-Hatem V, Denninger MH, Boucekkine T, Debzi N. Aetiological factors of Budd-Chiari syndrome in Algeria. *World J Hepatol* 2015; **7**: 903-909 [PMID: 25937867 DOI: 10.4254/wjh.v7.i6.903]

99 **Darwish Murad S**, Plessier A, Hernandez-Guerra M, Fabris F, Eapen CE, Bahr MJ, Trebicka J, Morard I, Lasser L, Heller J, Hadengue A, Langlet P, Miranda H, Primignani M, Elias E, Leebeek FW, Rosendaal FR, Garcia-Pagan JC, Valla DC, Janssen HL; EN-Vie (European Network for Vascular Disorders of the Liver). Etiology, management, and outcome of the Budd-Chiari syndrome. *Ann Intern Med* 2009; **151**: 167-175 [PMID: 19652186 DOI: 10.7326/0003-4819-151-3-200908040-00004]

100 **Plessier A**, Esposito-Farèse M, Baiges A, Shukla A, Garcia Pagan JC, De Raucourt E, Ollivier-Hourmand I, Cervoni JP, De Ledinghen V, Tazi Z, Nousbaum JB, Bun R, Bureau C, Silvain C, Tournilhac O, Gerfaud-Valentin M, Durand F, Goria O, Tellez L, Albillos A, Gioia S, Riggio O, De Gottardi A, Payance A, Rautou PE, Terriou L, Charbonnier A, Elkrief L, de la Tour RP, Valla DC, Gault N, de Fontbrune FS. Paroxysmal nocturnal hemoglobinuria and vascular liver disease: Eculizumab therapy decreases mortality and thrombotic complications. *Am J Hematol* 2022; **97**: 431-439 [PMID: 35049058 DOI: 10.1002/ajh.26474]

101 **Randi ML**, Tezza F, Scapin M, Duner E, Scarparo P, Scandellari R, Fabris F. Heparin-induced thrombocytopenia in patients with Philadelphia-negative myeloproliferative disorders and unusual splanchnic or cerebral vein thrombosis. *Acta Haematol* 2010; **123**: 140-145 [PMID: 20134155 DOI: 10.1159/000280466]

102 **Zaman S**, Wiebe S, Bernal W, Wendon J, Czuprynska J, Auzinger G. Increased prevalence of heparin-induced thrombocytopenia in patients with Budd-Chiari syndrome: a retrospective analysis. *Eur J Gastroenterol Hepatol* 2016; **28**: 967-971 [PMID: 27015137 DOI: 10.1097/MEG.0000000000000632]

103 **Semmler G**, Lindorfer A, Schäfer B, Bartl S, Hametner-Schreil S, Gensluckner S, Balcar L, Pomej K, Lampichler K, Trauner M, Aigner E, Datz C, Zoller H, Hofer H, Schöfl R, Mandorfer M, Reiberger T, Scheiner B. Outcome of Budd-Chiari Syndrome Patients Treated With Direct Oral Anticoagulants: An Austrian Multicenter Study. *Clin Gastroenterol Hepatol* 2023; **21**: 978-987.e2 [PMID: 35533994 DOI: 10.1016/j.cgh.2022.04.024]

104 **Sharma S**, Kumar R, Rout G, Gamanagatti SR, Shalimar. Dabigatran as an oral anticoagulant in patients with Budd-Chiari syndrome post-percutaneous endovascular intervention. *J Gastroenterol Hepatol* 2020; **35**: 654-662 [PMID: 31476024 DOI: 10.1111/jgh.14843]

**Footnotes**

**Conflict-of-interest statement:** All authors declare no conflict of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** June 27, 2023

**First decision:** July 25, 2023

**Article in press:** August 17, 2023

**Specialty type:** Gastroenterology and Hepatology

**Country/Territory of origin:** Italy

**Peer-review report’s scientific quality classification**

Grade A (Excellent): A

Grade B (Very good): B, B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Harmanci O, Turkey; Pintar T, Slovenia; Qi XS, China **S-Editor:** Lin C **L-Editor:** A **P-Editor:** Yu HG

**Table 1 Characteristics of studies on non-cirrhotic patients with portal vein thrombosis treated with direct oral anticoagulants**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study** | **Population** | **Outcomes** | **Adverse events** | **Ref.** |
| Prospective | Non-cirrhotic, atypical sites (including PVT); Riva and Api for PVT (*n* = 16) *vs* enoxa for PVT (*n* = 13) | Riva and Apixaban are effective and safe in patients with venous thrombosis of atypical locations | No major difference in bleeding rate | Janczak *et al*[40], 2018 |
| Retrospective | Non-malignant PVT, both cirrhotic and non-cirrhotic; Edo (*n* = 4), Api (*n* = 3), Riva (*n* = 2), Dabi (*n* = 1) *vs* traditional AC (*n* = 12), no AC (*n* = 39) | Favourable outcomes with DOACs with regression/resolution of thrombus in 20% of patients and stability or nonprogression in 80% | One bleeding episode in DOACs | Scheiner *et al*[41], 2018  |
| Retrospective | Non-cirrhotic PVT; Riva (*n* = 65), Api (*n* = 20), Dabi (*n* = 8) *vs* Warf (*n* = 108), Enoxa (*n* = 70), Fondap (*n* = 2) | Resolution rate: Dabi (75%), Api (65%), Riva (65%), Enoxa (57%), Warf (31%)； Recanalization rates are higher in DOACs compared to Warf but similar to Enoxa | Less major bleeding incidence in DOACs | Naymagon *et al*[42], 2020 |
| Retrospective | IBD-associated PVT; DOACs (*n* = 23) *vs* Warf (*n* = 22), Enoxa (*n* = 13) | Resolution rate: DOACs (96%), Warf (55%); DOACs group needed a shorter course of anticoagulation (median 3.9 *vs* 8.5) | N/A | Naymagon *et al*[43] 2021 |
| Retrospective | Intraabdominal surgery < 3 mo prior to PVT diagnosis; DOACs (*n* = 35) *vs* Warf (*n* = 31), Enoxa (*n* = 29), no AC (*n* = 12) | Complete resolution rate: DOACs (77%), Enoxa (69%), Warf (45%), no AC (17%) | N/A | Naymagon *et al*[44], 2021 |
| Retrospective | PVT with/without cirrhosis; DOACs (*n* = 13; 8 non-cirrhotic) *vs* Warf (*n* = 20; 15 non cirrotic) | Treatment failure: DOACs (*n* = 0); Warf (*n* = 4) | Major bleedings: DOACs: *n*=0; VKA: *n*=1 | Ilcewicz *et al*[45], 2021 |
| Prospective | SVT without cirrhosis; Riva 15 BID for 3 wk + Riva 20 mg OD for 3 mo (*n* = 100) | Recanalization > 80% at 3 mo (47% complete) | 2 major bleeding; 2 SVT recurrence | Ageno *et al*[46], 2022 |

AC: Anticoagulation; Api: Apixaban; BID: Twice daily; Dabi: Dabigatran; DOACs: Direct oral anticoagulants; Edo: Edoxaban; Enoxa: Enoxaparin; Fondap: Fondaparinux; IBD: Inflammatory bowel disease; OD: Once daily; PVT: Portal vein thrombosis; Riva: Rivaroxaban; SVT: Splanchnic vein thrombosis; VKA: Vitamin K antagonists; Warf: Warfarin.

**Table 2 Comparison of main clinical practice guidelines for the management of portal vein thrombosis in non-cirrhotic patients**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **EASL 2016[30]**  | **AASLD 2020[38]**  | **ACG 2020[52]**  | **Baveno VII 2022[35]** |
| Classification | Acute; Chronic | Recent: < 6 mo; Chronic: > 6 mo | Acute; Chronic | Recent: < 6 mo; Chronic: > 6 mo |
| Treatment | Acute: AC; Chronic: Not specified | Recent PVT: AC; Chronic complete PVT or cavernous transformation: No benefit from AC | Acute PVT: AC; Chronic: thrombophilia, progression of thrombus into mesenteric veins, current or previous evidence of bowel ischemia | Recent PVT: At diagnosis; Chronic PVT: After prophylaxis for portal hypertensive bleeding in high-risk varices |
| Choice of anticoagulation | LMWH, VKA | LMWH, VKA, DOACs | UFH, LMWH for initiation; LMWH or VKA for maintenance (DOACs absorption limited in the presence of intestinal oedema) | LMWH, VKA, DOACs |
| Duration of treatment | At least 6 mo in presence of transient risk factor; long term for persistent risk factor or in case of chronic PVT with history of intestinal ischemia or recurrent thrombosis | AC for 3 mo | At least 6 mo for acute without thrombophilia; long term with thrombophilia | Recent PVT: At least 6 mo; Chronic: Long term for patient with permanent prothrombotic state |
| Notes |  |  |  | EVL can be performed safely without withdrawing VKA |

AASLD: American Association for the Study of Liver Diseases; AC: Anticoagulation; ACG: American College of Gastroenterology; DOACs: Direct oral anticoagulants; EASL: European Association for the Study of the Liver; EVL: Endoscopic variceal ligation; LMWH: Low molecular weight heparin; PVT: Portal vein thrombosis; UFH: Unfractioned heparin; VKA: Vitamin K antagonists.

**Table 3 Characteristics of studies on cirrhotic patients with portal vein thrombosis treated with direct oral anticoagulants**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Population** | **Aim of study** | **Doses and duration** | **Outcomes** | **Adverse events** | **Ref.** |
| Retrospective | Cirrhotic, CP A/B/C; any indication (incl. PVT); subgroup with PVT: Riva or Api (*n* = 4) *vs* Enoxa or VKA (*n* = 3) | Efficacy and safety of DOACs *vs* traditional AC in cirrhosis | Riva 15 mg OD +/- 20 mg OD load; Api 5 mg BID +/- 10 mg BID load 10.6 mo (mean) | Recurrent thrombosis: DOACs (*n* = 1); Trad AC (*n* = 1) | Total bleeding events were similar in the two groups (with lesser major bleeding in the DOACs group) | Hum *et al*[87], 2017 |
| Retrospective | Cirrhotic, CP A/BAny indication (incl. PVT); subgroup with PVT: Riva or Api (*n* = 12) *vs* LMWH or Warf (*n* = 6) | Compare the bleeding rates in cirrhotic patients | Riva 20 mg OD; Api 5 mg BID 10.6 mo (mean) | No statistical difference between therapeutic and prophylactic dosing between groups | Similar rates of major and minor bleeding in the two groups | Intagliata *et al*[89], 2016 |
| Retrospective | Both cirrhotic and non, CP A/B; any indication (incl. PVT); subgroup with cirrhosis and PVT: Riva, Api or Dabi (*n* = 22) | Indication for starting or switching to DOACs and report short-term efficacy and safety | Cirrhotic: Different doses 9.6 mo (mean) | Cirrhotic: recurrent PVT (*n* = 1, 4.5%) | Cirrhotic group any indication: Major bleeding (*n* = 1), minor bleeding (*n* = 4) | De Gottardi *et al*[88], 2017 |
| Retrospective | Both cirrhotic and non, CP A/B/C; non-malignant PVT; Edo (*n* = 4), Api (*n* = 3), Riva (*n* = 2), Dabi (*n* = 1) *vs* traditional AC (*n* = 12), no AC (*n* = 39) | Efficacy and safety of AC in non-malignant PVT | Edo 30/60 mg OD, Api 5 mg BID, Riva 10 mg OD, Dabi 110 mg BID 9.2 mo (median) | Favourable outcomes with DOACs: Regression/resolution 20%; stability/non-progression 80% | Portal hypertensive gastropathy bleeding | Scheiner *et al*[41], 2018 |
| Retrospective | Cirrhotic, CP A/B; non-malignant PVT; Edo (*n* = 20) *vs* Warf (*n* = 30) (following 2 wk Danaparoid) | Compare the efficacy and safety of Edo and Warf for treatment of chronic PVT in cirrhotic patients | Edo 60 mg OD, (if CrCl > 50; *n* = 4) or Edo 30 mg OD (if CrCl < 50; *n* = 16) 6 mo (max) | Edo group had more complete resolution and less PVT progression than Warf group | Major GI bleeding: Edo (*n* = 3; 7%); Warf (*n* = 2; 15%) | Nagaoki *et al*[91], 2018 |
| Prospective | Cirrhotic, CP A; chronic PTV; Riva (*n* = 26), Dabi (*n* = 14) *vs* no AC (*n* = 40) | Compare the efficacy and safety of DOACs and no AC in chronic PVT in cirrhotic patients | Riva 20 mg OD; Dabi 150 mg BID; 6 mo (max) | Recanalization rate with DOACs 28.2% (statistically higher) and improvement of liver function | No statistically significant difference between the DOACs and the control group in bleeding events | Ai *et al*[92], 2020 |
| Prospective | Cirrhotic, CP A/B/C; non-malignant PVT; TIPS + AC (*n* = 197, 18 Riva) *vs* AC only (*n* = 63, 4 Riva) *vs* TIPS only (*n* = 88) *vs* nothing (*n* = 48) | Compare the management using a wait-and-see strategy, AC, and TIPS to treat PVT in cirrhosis | Riva 10 mg OD; 21.0 mo (median) | Recanalization: 0% with Riva only (all with PVT and SMV thrombosis), 100% with Riva + TIPS | Major bleeding events: AC only (*n* = 14); TIPS+AC (*n* = 30) | Lv *et al*[93], 2021 |

AC: Anticoagulation; Api: Apixaban; VKA: Vitamin K antagonists; BID: Twice daily; CP: Child-Pugh score; Dabi: Dabigatran; DOACs: Direct oral anticoagulants; Edo: Edoxaban; GI: Gastrointestinal; Enoxa: Enoxaparin; LMWH: Low molecular weight heparin; OD: Once daily; PVT: Portal vein thrombosis; Riva: Rivaroxaban; SMV: Superior mesenteric vein; TIPS: Transjugular intrahepatic portosystemic shunt; Warf: Warfarin.



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2023 Baishideng Publishing Group Inc. All rights reserved.**