Reviewer #1:

1. Page 3 line 39: “thrombofilic” should be changed to “thrombophilic” 2. Page 3 line 48: “unfractioned” should be replaced by “unfractionated” 3. Page 7 line 175: “patients” should be changed into “patient” 4. Reference styling in manuscript and under reference list is not compatible with WJG standards. This should be revised accordingly.

Thanks for your suggestions. We corrected all the typos and we performed a further English editing. Reference styling has been changed according to WJG standards.

Reviewer #2:

1. Many other potentialsitautions are related to portosistemic thrombosis; there is a growing evidence in the literature that portosistemic thrombosis might be related to surgical interventions, genetic factors and others. The presentation of clinical relevance is important. 2. Astract should clearly present the clinical relevance of prompt medical interventions. 3. New cornerstone treatment options are availabe; important to mentione clot aspiration by interventional radiologist. The time frame for better clinical outcome is mandatory to discuss and mentione. 4. The authors shoul comment and discuss cancer related SVT an portosystemic thrombosis. 5. Authors should comment heparin dose adjustment in case of renal imairment and other clinical circumstances influencing mandatory dose adjustment. Besides, other therapeutic approach is needed to be expalined. 6. Authors should comment DOAC in liverand kidney function impairment. 7. In terms of risk factors, it would also be useful to mention the increased risk of portosystemic thrombosis in the case of certain viral diseases, which has been shown to be associated with infection with COVID19 and others. 8. I recommend the comments in the description of cavernous transformation of the porta, including consequences (portal hypertension), measures (TIPS) and increased risk of portosystemic thrombosis. 9. line 130-141: Having said this, the authors should be reminded of the very small number of DOAC-treated subjects observed, and commentary should be very limited in view of this fact. 10. line 147-151: In the paper, the authors should present the increased risk of thromboembolic complications in patients with IBD a little more precisely, including the increased risk with some types of therapy. 11. line 180-187: Due to the importance of the content of the paper, authors should indicate the risk of PST according to Child grade or other classification systems that define liver cirrhosis. 12. line 231: The authors should define the risk of PST in case of altered biliary derivation (external biliary drainage) and DOAC treatment. 13. line 250-299: It would be very important for the reader to know the inclusion criteria when deciding to introduce DOACs, as far as the studies state this; random introduction significantly reduces the strength of the evidence and thus could lead to irrelevant conclusions.

Thank you for all your valuable suggestions.

As recommended in *point 13*, we have described in more detail the cited studies. This implementation will certainly give the readers more information for critically analyze results currently available in the literature.

About *point 9*, we totally agree with you that the small number of patients treated with DOAC did not allow to give strong recommendations. As a review of the literature, we reported the results given in the original articles; we tried to highlight the limitations (such as small sample size) we noticed after a careful reading of these papers. Since the majority of works in the literature has small sample size (<20 pts treated with DOACs), we decided not to stress this point at the end of each study presentation to avoid being repetitive. We have already talk about this limitation at the end of each paragraph (lines 191-192, 340-341), and we also added a sentence in the "conclusion" paragraph (line 398).

About *point 4*, there are lots of papers on DOACs and CAT (cancer-related thrombosis), but they are generally based on thrombosis in usual sites (i.e. DVT).
Among the studies we cited, there are also patients with non-malignant cancer-related SVT (mainly PVT), but authors did not perform subgroup analysis so we cannot report results on efficacy and safety for these patients. (e.g. line 301-302).
In real-life, DOACs are used in cancer patients for thrombosis in unusual sites and we suppose an acceptable level of safety and efficacy. We agree with you that information on this topic could be very useful in the clinical practice, but unfortunately it is lacking at the moment.

About *point 12*, we did not find any article (not case reports) dealing with external biliary drainage-related SVT treated with DOACs. If you are aware of any potential manuscript on this subject, please let us know and we will be pleased to add it in our review.

About the remaining points, we would like to make one thing clear. The aim of our review is reporting all the available evidence about the use of DOACs for the treatment of SVT, that is still a field with a high level of uncertainty even for expert angiologists that deal with these drugs daily.
We do not have the ambition of neither writing a clinical practice guideline about diagnosis and management of SVT (we cited the current available guidelines and a recent and exhaustive review on this topic - doi: 10.1016/j.jhepr.2022.100667) nor giving a dosing schedule vademecum for

anticoagulation therapy (standard and adjusted dosing for heparins, AVK and DOACs are widely known).

We have deliberately withheld the other possible approaches for SVT and its complications (e.g. TIPS, Meso-Rex shunt, suction thrombectomy, thrombolysis, angioplasty, non-selective beta-blockers…) because their extensive discussion would have gone beyond the main aim of this review. For the same reason we did not want to deeply describe the pathogenesis and all the potential etiologies of SVT. Anyway, we added some sentenced in the "introduction" paragraph in order to enrich it (lines 48-54).

Some of the requested revisions were already presented in the main text; please refer to lines 41-44, 45-47, 89-101, 106-109, 110-114, 123-128, 191-192, 216, 245-257, 340-341, 350-357.

Reviewer #3:

An interesting topic. I recommend its potential publication in this journal. The authors should improve the language and grammar. Some minor comments are listed as follows. 1. In page 3, the authors said "Cirrhotic patients generally presents a PVT with an incidence that ranges from 11% to 24% at 5 years", where the word "presents" should be revised as "present". 2. In page 6, the authors said "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 e VKA groups", where the word "e" should be revised as "and". 3. In page 7, the authors said "The recanalization rate at 3 months was achieved in more than 80% of patients", where the word "rate" should be removed. 4. In page 8, the authors said "safety and efficacy of anticoagulation seems to be similar to patients without hepatocellular carcinoma", where the word "seems" should be revised as "seem". 5. In page 8, the authors said "In the last few years, experience with DOACs is growing also in the setting of cirrhotic patients", where the word "also" should be replaced before the word "growing". 6. In page 9, the authors said "Of note, results presented by authors are referred to the entire population of study; despite the majority of patients presented a PVT, actual conclusions on these patients cannot be extrapolated". A full stop is lacking at the end of the sentence.

Thanks for your suggestions. We corrected all the typos and we performed a further English editing.

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

Giovanni Monaco[1,2], Luca Bucherini[3], Bernardo Stefanini[1,2], Fabio Piscaglia[1,2], Francesco Giuseppe Foschi[3], Luca Ielasi[3]

Affiliations

1 - Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
2 - Division of Internal Medicine, Hepatobiliary and Immunoallergic Diseases, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy
3 - Department of Internal Medicine, Ospedale degli Infermi di Faenza, Faenza, Italy.

Corresponding author:

Luca Ielasi, MD, Department of Internal Medicine, Ospedale degli Infermi di Faenza, Faenza, 48018, Italy. luca.ielasi.kr@gmail.com

Keywords:

Splanchnic vein thrombosis; SVT; portal vein thrombosis; PVT; Budd-Chiari syndrome; BCS; direct oral anticoagulants; DOACs.

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.

Core Tip

The term splanchnic vein thrombosis (SVT) includes portal vein thrombosis (PVT) and Budd-Chiari syndrome (BCS). 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 ~~and encouraging~~ 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 ~~and with~~ underlying liver disease. (1)

In the first case, SVT represents a rare condition with a prevalence of less that 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 ~~thrombofilic~~ thrombophilic risk factors is uncommon. Cirrhotic patients generally ~~presents~~ 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 ~~frequent~~; 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 ~~unfractioned~~ unfractionated heparin (UFH) due to its lower incidence ~~rate~~ of heparin-induced thrombocytopenia, unless there are contraindications to LMWH such as severe renal failure ~~in case of LMWH contraindications such as severe renal dysfunction.~~ 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 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, ~~being orally taken at fixed doses, having a~~ 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 ~~in this setting~~ 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 portal vein thrombosis

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) SARS-CoV-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 ~~like~~ 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 months 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 ~~like~~ such as intestinal infarction and the development of portal hypertension. ~~Acute PVT seldom resolves spontaneously~~ 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 ~~Consequently, treatment should be started at diagnosis with anticoagulation at a full-dose~~. (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 months 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, ~~and~~ 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)

~~Concerning the anticoagulant choice, LMWH with subsequent switch to VKA have the most evidence for PVT treatment, and therefore still represents the established therapy for most patients, given at the same therapeutic regimens and with the same dose adjustments as for typical site venous thromboembolism.~~

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.

~~Recently,~~ 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. 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. performed a ~~respective~~ retrospective study with 51 cirrhotic patients with ~~and without liver cirrhosis and~~ concomitant non-malignant PVT. No anticoagulation therapy was started in 39 patients, whereas ~~warfarin in~~ 12 patients received warfarin. Additionally, they also enrolled ~~whereas~~ 10 patients ~~were shifted to~~ treated with DOACs after traditional anticoagulation. In particular, 4 patients received edoxaban 30 or 60 mg OD, 3 apixaban 5 mg BID, 2 rivaroxaban 10 mg OD, 1 dabigatran 100 mg BID. The mean follow-up time was 9.2 months. 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. ~~Because~~ Since cavernous transformation of the chronic PVT was already present in all patients treated with DOACs (therefore achieving recanalization could be difficult ~~difficultly be achieved~~), 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 ~~e~~ and VKA groups. (41)

Naymagon et al. 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. 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.* conducted the first interventional study evaluating the safety and efficacy of DOACs in non-cirrhotic PVT. ~~It~~ 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 twice daily for 3 weeks followed by 3 months of rivaroxaban 20 mg once daily. Major bleeding was the primary endpoint of the study; secondary endpoints included death, recurrent SVT, and complete vein recanalization within 3 months. 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 ~~rate~~ at 3 months 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 portal vein thrombosis

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, ~~consequently~~ (i.e., portal hypertension); the blood stasis together with ~~a~~ 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 months) and >50% occlusive thrombosis of the main portal vein trunk, in those with symptomatic PVT or in potential candidates for liver transplantation. In the ~~latter~~ 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 months; 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 (35,30,52,38) 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, ~~and~~ 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*. reporting no difference in major and minor bleeding rates between patients with or without anticoagulation therapy for PVT. (56) 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 ~~seems~~ 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)

~~In the last few years, experience with DOACs is growing also in the setting of cirrhotic patients.~~ 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 ~~its~~ 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.* published a randomized controlled trial on rivaroxaban 10 mg bid vs warfarin, but it has been recently retracted for methodological issues, (86) therefore it will not be considered in our review.

First data were obtained by *Hum et al*. 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*. 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. 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 months. 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. ~~Of note, results presented by authors are referred to the entire population of study; despite the majority of patients presented a PVT, actual conclusions on these patients cannot be extrapolated.~~ 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. (88)

Another study examining DOACs safety in cirrhosis, but this time in comparison with conventional anticoagulants, was conducted by *Intagliata et al*. 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. (89)

Also *Davis et al*. 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. (90)

Nagaoki et al. 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 months, respectively). Complete recanalization, assessed by CT scan at 6 months, 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*. 80 patients with cirrhosis and chronic PVT were examined. Patients with history of recent bleeding (<3 months), high risk esophageal varices, systemic malignancies, severe renal impairment (creatinine clearance <30 ml/min), concomitant antiplatelet therapy and low platelet count ($<50 \times 10^9$/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 months. The recanalization rate was higher in the DOAC group than in the control group, especially after 6 months of treatment (12.8% at 3 months versus 28.2% at 6 months), 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*. 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 months 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.

Budd-Chiari syndrome

Causes of primary BCS are essentially the same of non-cirrhotic PVT. (16) Compared with PVT, there is a ~~higher~~ greater prevalence of ~~relationship~~ 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 ~~they~~ 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*. 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, ~~so~~ it is not possible to extrapolate conclusions about efficacy and safety in this cohort of patients. (88)

A recent multicentric Austrian study ~~tried~~ 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 ~~shifting~~ switching to DOAC.

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

~~Third~~ 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*., 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 months. (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.

Conclusions

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 ~~of study~~, 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.

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Tables and Figures

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

Study	Population	Outcomes	Adverse Events
Janczak et al. 2018 Prospective (40)	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.
Scheiner et al. 2018 Retrospective (41)	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
Naymagon et al. 2020 Retrospective (42)	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. 2020 Retrospective (43)	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. 2020 Retrospective (44)	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
Ilcewicz et al. 2020 Retrospective (45)	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

Ageno et al. 2022 Prospective (46)	SVT without cirrhosis Riva 15 BID for 3 wk + Riva 20 mg OD for 3 mo (n=100)	Recanalization >80% at 3 months (47% complete)	2 Major bleeding 2 SVT recurrence

AC: anticoagulation; DOACs: direct oral anticoagulants; IBD: inflammatory bowel disease; LMWH: low-molecular-weight heparin; PVT: portal vein thrombosis; SMV: superior mesenteric vein; SVT: splanchnic vein thrombosis; VKA: vitamin K antagonists.

Drugs abbreviations: Api: apixaban; Dabi: dabigatran; Edo: edoxaban; Enoxa: enoxaparin; Fondap: fondaparinux; Riva: rivaroxaban; 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 months Chronic: > 6 months	Acute Chronic	Recent: < 6 months Chronic: > 6 months
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 months 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 months	At least 6 months for acute without thrombophilia Long term with thrombophilia	Recent PVT: at least 6 months Chronic: long term for patient with permanent prothrombotic state
Notes				EVL can be performed safely without withdrawing VKA

AC: anticoagulation; DOACs: direct oral anticoagulants; EVL: endoscopic variceal ligation; LMWH: low molecular weight heparin; PVT: portal vein thrombosis; UFH: unfractioned heparin; VKA: vitamin K antagonists.

795 **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
Hum et al. 2016 Retrospective (87)	Cirrhotic, CP A/B/C Any indication (incl. PVT) Subgroup with PVT: Riva or Api (n=4) *vs* Enoxa or AVK (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)
Intagliata et al. 2016 Retrospective (89)	Cirrhotic, CP A/B Any 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.
De Gottardi et al. 2017 Retrospective (88)	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)
Scheiner et al. 2018 Retrospective (41)	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.
Nagaoki et al. 2018 Retrospective (91)	Cirrhotic, CP A/B non-malignant PVT Edo (n=20) *vs* Warf (n=30)	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)	Edo group had more complete resolution and less PVT progression than Warf group	Major GI bleeding: Edo (n=3; 7%) Warf (n=2; 15%)

	(following 2 wk Danaparoid)		6 mo (max)		
Ai et al. 2020 Prospective (92)	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
Lv et al. 2021 Prospective (93)	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).

AC: anticoagulation; CP: Child-Pugh score; DOACs: direct oral anticoagulants; GI: gastrointestinal; HCV: hepatitis C virus; PVT: portal vein thrombosis; SMV: superior mesenteric vein; TIPS: tranjugular intrahepatic postosystemic shunt; VKA: vitamin K antagonists.

Drugs abbreviations: Api: apixaban; Dabi: dabigatran; Edo: edoxaban; Riva: rivaroxaban; Warf: warfarin