57 Anticoagulation in Splanchnic Vein Thrombosis With and Without Underlying Liver Disease

Marco Senzolo and Alberto Zanetto

Introduction

The occurrence of thrombosis in the liver venous vessels is determined by an alteration in the physiological equilibrium that regulates the balance between coagulation and anticoagulation. As hypercoagulability plays a major role in the pathophysiology of splanchnic and hepatic vein thrombosis, anticoagulation is a cornerstone in the treatment of these patients, including those with cirrhosis. This chapter reviews the current knowledge regarding anticoagulation in splanchnic and hepatic vein thrombosis.

Budd–Chiari Syndrome

The use of anticoagulation became systematic from the mid-80s with the comprehension of thrombophilic conditions associated with Budd–Chiari syndrome (BCS) [1]. Early studies showed that Factor V Leyden was present in up to 20% of patients [2]. Later studies confirmed that JAK2 V617F mutation was found in 60% of cases (24/41) [3]. The widespread adoption of anticoagulants led to the improvement in patient's survival [1]. Yet, preliminary reports showed that only a minority of anticoagulated patients (approximately 30%) achieved resolution/stabilization of thrombosis [4, 5]. Different radiological and surgical treatments were proposed and combined with anticoagulation, and this finally led to the stepwise algorithm which is currently recommended [6, 7].

According to this algorithm, anticoagulation must be initiated as early as possible after diagnosis. All patients should be treated, including those without an underlying prothrombotic disorder and those who are asymptomatic [8]. The aim of

M. Senzolo (✉) · A. Zanetto
Gastroenterology and Multivisceral Transplant Unit, Department of Surgery, Oncology, and Gastroenterology, Padua University Hospital, Padua, Italy

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anticoagulation is to restore hepatic vein outflow or, at least, prevent progression of thrombosis, which can be achieved in approximately 15%–25% of patients, particularly in those with mild/moderate disease [9, 10]. In patients without ongoing improvement and in those with progression of thrombosis despite anticoagulation, additional interventions will be considered. Consensus on how to define lack of response to anticoagulation has not yet been reached. Some criteria were proposed to define treatment failure and identify the optimal timing at which to move a patient along the algorithm (Table 57.1); however, they lack prospective validation [6].

Anticoagulation should start with low-molecular weight heparin (LMWH) and then be switched to long-term vitamin K antagonists (VKA), with the goal of maintaining the INR > 2.5 [8]. Intravenous heparin should be avoided because of the association between BCS and myeloproliferative disease (MPD), which increases the risk of heparin-induced thrombocytopenia (HIT) (10% in a previous study including 58 JAK2V617F-positive patients) [11]. Increased level of platelet activation markers has been reported in heparin-treated patients, which could explain the predisposition for HIT due to formation of PF4/heparin complexes [12]. In the same way, HT has been reported in patients with polycythemia vera (PV) and essential thrombocythemia (TE). Randi et al. [13] reported that among 29 patients with MPD treated with heparin, 5 (17%) developed a new clinically significant thrombotic complication between 11 and 55 days after start of heparin therapy. Among these five patients (two with PV and three with TE), 40% had unequivocal HT.

Lifelong anticoagulation is recommended to reduce the risk of thrombosis recurrence [8]. De Stefano and colleagues retrospectively studied 181 patients who presented a first episode of splanchnic vein thrombosis (67 with PV, 67 with TE, and 47 with primary myelofibrosis) [14]. BCS and portal vein thrombosis (PVT) were diagnosed in 31 (17%) and 109 (60%) patients, respectively, while isolated thrombosis of mesenteric or splenic veins was detected in 18 (10%) and 23 (13%) cases,

Table 57.1 Evaluation of response to treatment in patients with BCS

	Ongoing treatments response (2 weeks)	Complete treatment response
Ascites	Yes	No clinically detectable
Creatinine	Normal or improving	Normal
Na^+	Normal of improving	Normal
Balance (water-Na^+)	Negative	
NaCl intake	Moderate	Moderate
Factor V	Improving	Above 40% of normal reference
Direct bilirubin	Improving	Below 15 mmol/L
Portal hypertensive-related bleeding	–	No
Spontaneous bacterial infections	–	No
Body mass index	–	>20 kg/m^2

Adapted from Plessier et al. [6]

respectively. After this index event, patients were followed for 735 patient years and experienced 31 recurrences corresponding to an incidence rate of 4.2 per 100 patient-years. Factors associated with a higher risk of recurrence were BCS (OR: 3.03), history of thrombosis (OR: 3.62), splenomegaly (OR: 2.66), and leukocytosis (OR: 2.8). VKA were prescribed in 85% of patients and the recurrence rate was 3.9 per 100 patient-years in treated patients, whereas in the small fraction (15%) not receiving VKA more recurrences (7.2 per 100 patient-years) were reported. In patients with prothrombotic disorders such as MPD, paroxysmal nocturnal hemoglobinuria, and Behcet's syndrome, specific treatment of these conditions is recommended to reduce the risk of thrombosis progression or recurrence [15–17].

BCS-associated MPDs are not absolute contraindications for LT [18–20]. However, LT does not cure most of the BCS-associated prothrombotic disorders and BCS may recur after LT. In a previous study of 36 patients with BCS who underwent LT, approximately 1/3 developed liver-related thrombotic complications and 10 of them needed re-transplantation [21]. Therefore, it is mandatory to start early anticoagulation after LT and maintain it life-long. The current approach is to use a combination including anticoagulation (VKAs), aspirin, and hydroxyurea (anti-proliferative drug) [22, 23]. In a previous series of patients with BCS who underwent LT, those with MPD (n = 12) treated with this combination showed a low risk of recurrence (8%), and thrombosis was not associated with graft dysfunction or reduced survival [23]. In recipients at risk of bleeding or who experience bleeding while on anticoagulation, it may be reasonable to avoid or stop VKAs and keep them on aspirin and anti-proliferative treatment. An exception for lifelong anticoagulation after LT could be considered in those recipients whose prothrombotic disorder is corrected by LT.

Patients with BCS on anticoagulation may be at risk of bleeding. In a prospective study including 94 patients with BCS, after a median follow-up of 43 months, 47 patients had 92 major bleeding episodes. Forty episodes were related to invasive procedures for BCS, while the origin of the other 52 episodes was gastrointestinal in 26 (including 15 related to portal hypertension) and genital in 10; 26 were spontaneous and 26 provoked. Excess anticoagulation was identified in 13 (27%) out of 49 documented episodes. These results indicate that invasive procedures and portal hypertension are the major drivers for bleeding in BCS, while excess anticoagulation plays a secondary role [24].

Few data on direct oral anticoagulants (DOACs) to treat BCS are available [25, 26]. DOACs may be considered in patients with BCS and normal liver function. However, DOACs are not registered for this indication, and if used, one should pay attention to potential comorbidities associated with BCS (i.e.: renal failure).

Portal Vein Thrombosis in Absence of Cirrhosis

Recent Portal Vein Thrombosis

Recent non-cirrhotic portal vein thrombosis (NCPVT) may present with varying degrees of severity [27]. Most patients with NCPVT only have modest and

non-specific symptoms; however, recent NCPVT can be rarely associated with significant morbidity and mortality. Mesenteric venous infarction is the most feared acute complication of NCPVT and may lead to perforation, peritonitis, and multiorgan failure. Early anticoagulation has lowered the incidence of this complication that is uncommon in anticoagulated patients (2% in a large multicenter study) [28]. In patients at risk for infarction but who do not show signs of peritonitis, interventional radiology may be an option [29]. These are patients with worsening abdominal pain despite 48 to 72 h of anticoagulation and in whom one would presume a lack of efficacy of anticoagulation. Anticoagulation, however, must be continued even after a successful radiological procedure. Previous data on the use of local thrombolysis have suggested a 60% rate of major bleeding [30]. A more recent series including 22 patients with NCPVT treated with a stepwise protocol (low-dose systemic alteplase followed by local clot dissolution therapy through a TIPS in patients with ongoing abdominal pain and no evidence of radiological improvement after 48–72 h of systemic thrombolysis) demonstrated a good rate of portal vein recanalization with no episode of intracranial bleeding [31]. Patients who show or develop peritoneal signs have to be evaluated for surgery. In patients who undergo intestinal resection, anticoagulation appears to improve the outcome [32].

The goal of treatment of NCPVT is to recanalize the obstructed veins, which will prevent intestinal infarction and portal hypertension. In a retrospective study, 50% of patients not achieving recanalization developed gastroesophageal varices, with a 2-year risk of variceal hemorrhage of 12%, and 16% developed ascites [33]. Severe portal biliopathy was observed in one/third of patients with NCPVT within 1 year after diagnosis [34, 35].

As spontaneous recanalization is very rare in untreated patients [33, 36], all NCPVT should be anticoagulated for at least 6 months. LMWH should be started early after diagnosis and then switched to VKA [8]. Unfractionated heparin is not recommended due to the high risk of HIT (20% in patients with MPD) [13]. It may be considered in special conditions such as glomerular filtration rate < 30 mL/min or pending procedures.

Two retrospective studies included consecutive patients with NCPVT treated with UFH or LMWH and switched to VKAs [33, 37]. If initiated immediately, anticoagulation led to recanalization in 40%–50% of patients. Bleeding complications were rare and mostly mild [33, 37]. By contrast, delays in anticoagulation (>1 week) were associated with a lower chance to achieve recanalization (20% vs. 60%) [33]. Among baseline factors, extension of thrombosis was associated with lower response to anticoagulation in one study [36] but not in another [33].

In 2010, Plessier et al. reported the first large, prospective multicenter study examining safety and efficacy of anticoagulation in 95 patients with NCPVT [28]. Patients received early of LMWH followed by VKAs targeting an INR of 2–3. Only 2% of patients developed intestinal infarction. Full recanalization was obtained in 38% of patients after 6 months of anticoagulation. Failure to achieve recanalization was independently related to ascites (HR 3.8) and splenic vein thrombosis (HR 3.5). A year after the diagnosis of NCPVT, 40% of the patients had permanent occlusion of portal vein and portal cavernoma. Bleeding was observed in 9% of the patients.

After a median follow-up of 8 months, mortality rate was 2% and was not related to bleeding or NCPVT [28].

DOACs have been sporadically used for the treatment of recent NCPVT [38, 39]. Recently, a retrospective study examining 330 patients with recent NCPVT treated with VKAs ($n = 108$), LMWH ($n = 70$), DOACs ($n = 93$), fondaparinux ($n = 2$), and no anticoagulation ($n = 57$) was published [40]. DOACs were associated with higher rate of complete thrombus resolution (HR 2.91) and lower rate of major bleeding (HR 0.20) compared with warfarin [40]. In another retrospective study looking at thrombosis recurrence and risk of bleeding in 26 patients with NCPVT treated with DOACs vs. 23 patients with NCPVT treated with enoxaparin, there was no difference in recurrent thrombosis and major bleeding between the two groups. Unfortunately, data regarding response to anticoagulation were not presented [38].

In patients with underlying thrombophilia, it is recommended to prolong anticoagulation independently of thrombosis resolution [8]. In a retrospective multicenter study including 109 patients with MPDs and NCPVT ($n = 63$) or BCS ($n = 46$), cytoreductive therapy was associated with a lower risk of liver-related events and vascular complications [15]. In NCPVT patients with paroxysmal nocturnal hemoglobinuria, eculizumab is indicated to achieve recanalization and prevent thrombosis recurrence [41].

Extrahepatic Portal Vein Obstruction (Chronic Portal Vein Thrombosis)

The aim of long-term anticoagulant therapy in extrahepatic portal vein obstruction (EHPVO) is to prevent thrombosis extension/recurrence and associated complications. Once prophylaxis for gastrointestinal bleeding has been implemented, we suggest considering permanent anticoagulation in patients with *any* prothrombotic condition, past history of intestinal ischemia, or in those with recurrent thrombosis during follow-up. This extends the previous recommendation by the European Association for the Study of the Liver [8], which considered permanent anticoagulation only in the presence of a *strong* prothrombotic condition, past history of intestinal ischemia or recurrent thrombosis on follow-up. No specific recommendation can be formulated for patients without persistent provoking factors.

The evidence regarding anticoagulation in patients with EHPVO is based on three-old retrospective studies [37, 42, 43] and two recent prospective cohorts [44, 45], which all suggest that long-term anticoagulation lowers the risk of thrombosis extension and recurrence. The impact of anticoagulation on patient's survival is not as clear as anticoagulation was independently associated with improved survival in one study [46] but not in other two [42, 43].

Condat et al. showed that anticoagulation in EHPVO was associated with a lower risk of mesenteric venous infarction (rate 0.82 and 5.2 per 100 patient-years in 84 treated vs. 52 non-treated patients, respectively) [42]. Similar results by Amitrano showed that the risk of recurrent thrombosis in treated patients was lower than in untreated patients (0% [0/10] vs. 46% [39/85]) [37].

In a recent international study including patients with splanchnic vein thrombosis (n = 604), the risk of recurrent thrombosis during a 2-year follow-up nearly doubled the risk of bleeding and risk of death related to thrombotic events was more than double than that related to bleeding [44]. Although the population was heterogenous due to inclusion of both patients with and without cirrhosis, the multivariate analysis in the subgroup of patients without cirrhosis (n = 437) showed that MPD and unprovoked SVT were independently associated with increased risk of vascular events (OR 9.02; $p = 0.01$ and OR 3.74; $p = 0.02$, respectively). On the other hand, anticoagulation reduced the risk of thrombosis (OR 0.88; $p < 0.001$) and was not associated with increased risk of major bleeding.

Current guidelines suggest that no anticoagulation should be given to patients with incidentally detected SVT [47]. By comparing patients with incidentally diagnosed SVT (n = 177) vs. those with clinically suspected PVT (n = 420) from the same multicenter registry, Riva et al. [45] demonstrated that the two conditions have similar clinical course and prognosis, which indirectly suggests that the same strategy should be considered in both groups. Unfortunately, this study did not exclude patients with cirrhosis and the higher number of cirrhotic patients in the incidentally detected group compared to the clinically suspected group (82/177 [46%] vs. 84/416 [20%], respectively; $p < 0.0001$) hinders the strength of the results.

The most frequent complication in patients with EHPVO is gastrointestinal bleeding related to portal hypertension [37, 42, 46]. Two retrospective studies show that long-term anticoagulation is not associated with increased risk of bleeding provided that prophylaxis is implemented prior to start of anticoagulation [37, 42]. Conversely, in another cohort in which a strategy for prophylaxis was not evaluated, anticoagulation was associated with a higher risk of bleeding (OR 2.0; $p = 0.01$) [43]. Yet, the severity of bleeding was not increased in treated vs. non-treated patients and recurrent thrombosis, but neither bleeding nor anticoagulation was associated with increased mortality (OR 3.1; $p = 0.02$) [43].

Current recommendation is therefore to start anticoagulation once prophylaxis for gastrointestinal bleeding is implemented [8]. However, preliminary data suggest that endoscopic variceal ligation (EVL) can be performed in patients with EHPVO without withdrawal of anticoagulation. No difference was found in a recent bicentric study between risk of post-EVL bleeding between patients who underwent EVL while on VKA vs. patients in whom anticoagulation was withdrawn (9 bleeding out of 121 session in 31 patients receiving VKA vs. 6 episodes out of 130 session in 13 patients not receiving VKA [48], similarly to patients with cirrhosis [49]).

Regarding DOACs, patients with SVT were excluded from phase III clinical trials and no large prospective study has yet investigated the safety of DOACs in the setting of EHPVO. The VALDIG consortium reported on the outcome of 38 patients with PVT without liver disease treated with different DOACs. After a median follow-up of approximately 26 months, 20% of patients (5/26) experienced side effects: 3 bleeding (1 VH, 1 due to gastric ulcer, and 1 prolonged menstrual bleeding) and 2 thrombosis (1 progressive PVT and 1 thrombosis of mesocaval shunt).

DOACs were stopped in four cases [50]. An independent study from North America compared three groups of patients: 63 patients with VTE in atypical locations (of whom 26 with SVT treated with rivaroxaban and apixaban), 23 patients with VTE (of whom 22 with SVT treated with enoxaparin), and 352 patients with VTE in typical locations treated with DOACs. Rates of recurrent thrombosis and major bleeding in patients receiving DOACs were comparable to those receiving traditional anticoagulation [38]. While awaiting prospective controlled studies, these preliminary data would suggest that DOACs may be considered for the treatment of patients with SVT.

Portal Vein Thrombosis in Cirrhosis

Portal vein thrombosis (PVT) in cirrhosis is a dynamic process and spontaneous recanalization may occur. Rate of recanalization ranges according to thrombosis and patient characteristics. In compensated patients with non-occlusive PVT, it is as high as 70% [51]. In decompensated patients with occlusive PVT, it is much lower (2% in a study including 42 patients with ascites) [52]. In decompensated patients or in those awaiting transplantation, partial PVT progresses in between 50% and 70% of patients at 2 years follow-up [52–54].

The influence of PVT on the risk of hepatic decompensation is still a matter of debate [55]. In compensated patients, partial PVT is not predictive of decompensation [51]. In decompensated patients, the impact of PVT on further decompensation is not as clear [56]. PVT may be asymptomatic and incidentally diagnosed at follow-up ultrasound; however, it may also be associated with risk of early treatment failure after VH [57], longer time to achieve variceal eradication, and higher risk of variceal relapse after eradication [58]. In addition, complete PVT has been related to a significantly higher post-liver transplant mortality [59].

Different treatment strategies have been adopted in cirrhosis complicated by PVT (Table 57.2) [53, 54, 56, 60–70, 73–75, 77]. There is no agreement on which drug should be used and the evidence is based on case series which show that recanalization rate varies between ~50% and ~75% (Table 57.2) [78]. In a recent meta-analysis including eight studies and 353 patients, a higher proportion of patients treated with anticoagulation had PVT recanalization compared with patients who were not anticoagulated (71% vs. 42%, respectively; $p < 0.0001$) [79]. Early start of anticoagulation (<6 months after PVT diagnosis) is the most important factor for predicting a response to therapy [8]. Involvement of mesenteric veins and/or the severity of cirrhosis have been reported as negative predictive factors for response [63, 75] but with conflicting results [56]. When anticoagulation is withdrawn, recurrence of thrombosis is frequent [73, 74]. Prolongation of anticoagulation treatment after recanalization may reduce the risk of re-thrombosis [53].

Cirrhosis is frequently associated with alterations of hemostasis [80–83] and there is still hesitation to anticoagulate these patients due to concerns of bleeding. However, current evidence does not show increased adverse outcomes in

Table 57.2 Published cohorts evaluating the efficacy of anticoagulant therapy for the treatment of portal vein thrombosis in patients with cirrhosis

Study	Patients (*n*)	Anticoagulation		PVT		
				Characteristics		Outcome
		T`ype	Duration (months)	Total/ partial	Extension to SMV/SV	No/partial/ complete recanalization
Retrospective						
Werner, 2013 [60]	28	VKA	12	NA	15	5/12/11
Chung, 2014 [61]	14	VKA	3.7	NA	3	3/5/6
Naeshiro, 2014 [62]	26	Daparanoid ± AT	0.5	NA	11	6/16/4
Chen, 2016 [63]	30[a]	VKA	7.6	NA	20	7/NA/NA
La Mura, 2018 [64]	63	VKA	23	15/48	32	19/13/31
Artaza, 2018 [65]	32	LMWH [29] VKA [3]	12	7/25	16	9/6/17
Scheiner, 2018 [66]	10	VKA	12	6/6	NA	2/1/7
Hayashi, 2019 [67]	52	Daparanoid ± AT	0.5	6/46	9	NA
Noronha-Ferreira, 2019 [68]	37	LMWH [15] VKA [22]	NA	NA	14	NA/18
Rodriguez-Castro, 2019 [69]	65[b]	LMWH	12	18/47	20	18/15/28
Pettinari, 2019 [70]	81	LMWH [56] Fondaparinux [15] VKA [10]	13.4	8/51[c]	29	35/15/31
Senzolo, 2021 [71]	124	FPX [41] LMWH [72]	8/12	43/81	14/41	21/18/61
Prospective						
Francoz, 2005 [54]	19	VKA	8.1	18/1	NA	11/0/8
Amitrano, 2010 [73]	28	LMWH	6	5/23	20	5/14/9
Delgado, 2012 [74]	55	LWMH [47] VKA [8]	7	14/41	27	22/8/25
Senzolo, 2012 [53]	33	LMWH	6	11/24	14	12/9/12
Cui, 2015 [75]	65	LMWH	6	11/54	NA	51/8/6

Table 57.2 (continued)

Study	Patients (*n*)	Anticoagulation		PVT		
				Characteristics		Outcome
		T`ype	Duration (months)	Total/ partial	Extension to SMV/SV	No/partial/ complete recanalization
Senzolo, 2018 [56]	92	UFH [6] LMWH [76] VKA [32]	6.5	NA	76	45/47[d]
Kwon, 2018 [77]	91	LMWH	5.7	14/77	38	32/36/20[e]

LMWH low-molecular weight heparin, *VKA* vitamin K antagonist, *UFH* unfractioned heparin, *AT* antithrombin, *NA* not available

[a] Although 30 patients were treated, only 22 had follow-up. Partial or total recanalization was seen in 15 patients, but differentiation between partial and total was not reported

[b] Anticoagulant treatment was suspended in four patients

[c] Include 22 patients with intra-hepatic thrombosis

[d] Includes both partial and complete recanalization

[e] Two patients were lost to follow-up

anticoagulated patients (Table 57.3) [53, 54, 56, 60–70, 73–75, 77]. A platelet count $<50 \times 10^9$/L and the use of VKA were the only factors related to bleeding in a previous study including 55 patients with cirrhosis and PVT [74]. Therefore, in patients with platelet counts $<50 \times 10^9$/L, LMWH may represent the best choice [84].

One concern regarding LMWH in cirrhosis is the reduction of plasmatic antithrombin, owing to the fact that LMWH requires antithrombin to exert its action. Unfortunately, anti-Xa assay (a test that is used to monitor LMWH activity) cannot be used in cirrhosis. Indeed, AT-deficient plasma, such that observed in cirrhosis, yields false anti-Xa determination due to decreased accuracy of classical anti-Xa assays [85]. In patients treated with VKA, a close monitoring of the INR is important to determine the therapeutic range and dosing of these drugs may be challenging due to preexisting elevations of INR. In a cohort study evaluating 29,000 INR measurements, liver disease and alcohol abuse were independently correlated with excessive anticoagulation [86].

Fondaparinux (FPX) has a linear pharmacokinetic profile with longer half-life, which allows once-daily administration, and does not bind to plasma proteins, which makes the development of immune thrombocytopenia unlikely [87, 88]. In a recent retrospective study comparing 124 patients with cirrhosis and PVT, 41 (33%) treated with FPX and 83 (67%) with LMWH, we found that FPX was associated with a higher probability of recanalization at 36 months. Interestingly, FPX remained effective also when used at lower dose due to coexisting thrombocytopenia. Yet, a higher bleeding rate observed in FPX-treated patients suggests caution in the use of FPX in cirrhosis [71].

DOACs that inhibit thrombin (dabigatran) or activated factor X (rivaroxaban, apixaban, edoxaban) are appealing alternatives. Advantages of DOACs include quick onset of action, oral administration, and no need for routine monitoring drug

Table 57.3 Bleeding episodes in patients with cirrhosis and portal vein thrombosis treated with anticoagulation

Study	Patients (n)	Child class (A/B/C)	Anticoagulation (type)	Adverse events associated with anticoagulation
Retrospective				
Werner, 2013 [60]	28	NA	VKA	1 vaginal bleeding
Chung, 2014 [61]	14	6/8/0	VKA	None
Naeshiro, 2014 [62]	26	13/8/5	Daparanoid ± AT	None
Chen, 2016 [63]	30	6/7/15	VKA	4 hematemesis; 1 epistaxis; 1 gingival bleeding
La Mura, 2018 [64]	63	28/35[a]	VKA	Major [8]: 5 GI bleeding; 1 intracranial bleeding; 1 hematoma; 1 hematuria; Minor [13]: 8 epistaxis; 1 lower GI bleeding; 1 anemia; 2 hematoma
Artaza, 2018 [65]	32	18/12/2	LMWH [29] VKA [3]	2 EV bleeding; 1 intracranial bleeding
Scheiner, 2018 [66]	10	NA	VKA	None
Hayashi, 2019 [67]	52	13/25/14	Daparanoid ± AT	None
Noronha-Ferreira, 2019 [68]	37	12/16/9	LMWH [15] VKA [22]	None
Rodriguez-Castro, 2019 [69]	65	27/23/15	LMWH	Major [2]: 1 intracranial bleeding; 1 congestive gastropathy; Minor [2]: 1 epistaxis; 1 hematuria
Pettinari, 2019 [70]	81	43/33/5	LMWH [56] FPX [15] VKA [10]	4 variceal bleeding, 6 hemorrhoidal bleeding; 2 GAVE; 4 post-traumatic.
Senzolo, 2021 [71]	124		FPX [41] LMWH [72]	22 episodes of bleeding, of whom 7 GI non-PH related; 3 VH; 1 post-paracentesis, and 1 intra-cranial
Prospective				
Francoz, 2005 [54]	19	2/13/4	VKA	1 EV bleeding after EVL
Amitrano, 2010 [73]	28	14/14[a]	LMWH	2 anemia secondary to portal hypertensive gastropathy requiring iron transfusion
Delgado, 2012 [74]	55	25/21/9	LWMH [47] VKA [8]	1 lower GI bleeding; 1 obscure gastrointestinal bleeding; 1 oral bleeding after dental extraction; 1 vaginal bleeding; 1 surgical wound hemorrhage

Table 57.3 (continued)

Study	Patients (n)	Child class (A/B/C)	Anticoagulation (type)	Adverse events associated with anticoagulation
Senzolo, 2012 [53]	33	11/16/8	LMWH	1 intracranial bleeding; 1 epistaxis; 1 variceal bleed; 1 hematuria
Cui, 2015 [75]	65	Pugh 7 (IQR 6–8)	LMWH	3 injections sites; 5 epistaxis; 2 hematuria
Senzolo, 2018 [56]	92	Pugh 7 (IQR 5–8)	UFH [6] LMWH [76] VKA [32]	Major [19]: 10 EV bleeding; 3 GI; 3 intracranial/intraspinal bleeding
Kwon, 2018 [77]	91	45/42/4	LMWH	Major [4]: 1 EV bleeding; 2 intracranial/intraspinal bleeding; 1 not specified; Minor [7]: not described

LMWH low-molecular weight heparin, *VKA* vitamin K antagonist, *UFH* unfractioned heparin, *FPX* fondaparinux, *NA* not available, *EV* esophageal varices, *EVL* esophageal variceal ligation, *GI* gastrointestinal, *GAVE* gastric antral vascular ectasia, *AT* antithrombin

[a] Includes both Child B and C

levels or effect. However, each agent has distinctive properties requiring particular attention to dosing, absorption, and clearance. Careful consideration of use of DOAC in patients with renal impairment is needed as DOAC are all dependent on renal clearance to varying degrees. Another issue to be aware, particularly for dabigatran and edoxaban, is the potential drug–drug interaction with NSBBs, statins, and PPIs [89, 90]. The volume of distribution of DOACs may vary according to body mass index and is different in underweight vs. obese patients. These conditions frequently occur in cirrhosis [91] and should be considered in prescribing or confirming DOACs in these patients [92]. In fact, a theoretical risk of excessive anticoagulation exists when using DOAC in cirrhosis and serum levels of DOACs are not sufficient for monitoring. However, Potze et al. demonstrated a decreased in vitro effect of rivaroxaban in patients with cirrhosis by using TG. In contrast, an increased response to dabigatran was found. Interestingly, the enhanced effect of dabigatran on TG was proportional to the severity of cirrhosis [93]. The same group examined the in vitro anticoagulant potency of apixaban [94]. Twenty-five ng/mL of apixaban or 50 ng/mL of rivaroxaban were added to plasma samples of 11 healthy individuals and 14 patients with cirrhosis (Child B and C). While a fixed dose of the drugs decreased total TG in healthy volunteers by 55 ± 6% (rivaroxaban) and 51 ± 4% (apixaban), the mean decrease in TG in cirrhosis was lower (30 ± 9% for rivaroxaban, $p < 0.0001$; 32 ± 10% for apixaban, $p < 0.0001$).

Although they are currently used off-label, some preliminary experiences have been reported (Table 57.4) [50, 95–98, 100]. The first retrospective case-series was described by Intagliata et al. [95] who looked at safety of DOACs in 20 patients with cirrhosis (Child A and B) treated with apixaban ($n = 11$) or rivaroxaban ($n = 9$). Indication for anticoagulation included PVT (approximately 2/3 of patients), atrial fibrillation, and non-splanchnic thrombosis. Median duration of AC was 270 days

Table 57.4 Published cohorts of patients with cirrhosis treated with direct oral anticoagulants

Study	Patients (n)	Patient characteristics	Anticoagulation			Adverse events
			Type	Duration (months)	Indication	
Intagliata, 2016 [95]	20	Child A [9] Child B [11] MELD 12 [10–15]	Rivaroxaban 10 mg or 20 mg [9] Apixaban 2.5 mg or 5 mg [11]	9	SVT [12] Non-splanchnic [4] Atrial fibrillation [4]	Major [1]: intracranial bleeding Moderate [1]: GI bleeding Mild [2]: GI bleeding and vaginal bleeding
De Gottardi, 2017 [50]	36	Child-Pugh 6 (range 5–8)	Rivaroxaban 15 mg [30] Apixaban 5 mg [4] Dabigatran 110 mg or 220 mg [2]	7	PVT [22] Concomitant BCS [5] Cardiac arrythmia [5] DVT [4]	Major [1]: lower GI Minor [4]: portal hypertensive bleedings, lower GI, epistaxis; post band ligation
Hum, 2017 [96]	27	Child A [11] Child B [12] Child C [4]	Rivaroxaban 15 mg with or without an initial 20 mg dose [17] Apixaban 5 mg, with or without an initial 10 mg dose [10]	7	Atrial fibrillation [15] DVT [12] PVT [4]	Major [1]; moderate [4]; minor [3]; 5/8 bleeding were GI-related)
Nagaoki, 2018 [97]	20	Child A [15] Child B [5]	Danaparoid for 2 weeks switched to edoxaban 60 mg [4] or 30 mg [16]	6	PVT	2 lower GI and 1 small bowel bleeding
Hanafi, 2019 [98]	40	HCV-cirrhosis Child A–B MELD 11 ± 1.4	LMWH for 3 days switched to rivaroxaban 10 mg	~3–7	PVT	None

Table 57.4 (continued)

Study	Patients (n)	Patient characteristics	Anticoagulation			Adverse events
			Type	Duration (months)	Indication	
Semmler, 2021 [99]	104	Child A [53] Child B [44] Child C [7]	Edoxaban in 59 patients Apixaban in 16 patients Rivaroxaban in 21 patients Dabigatran in 2 Sequential treatment in 6 61 (58.7% full dose) and 43 (41.3% reduced dose)	10.5	PVT [74] BCS [9] AF [15] AF and PVT [7] DVT/PE [6] Others [2]	6 procedure related bleedings (1 major and 5 minor) 33 spontaneous bleeding events

MELD model for end-stage liver disease, *PVT* portal vein thrombosis, *SVT* splanchnic vein thrombosis, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *BCS* Budd–Chiari syndrome, *GI* gastro-intestinal

[a] Dose unknown

and DOACs were given at full dose (10 mg apixaban or 20 mg rivaroxaban) in 15 patients and at lower dosages in 5 patients (5 mg apixaban or 10 mg rivaroxaban daily). Major bleeding occurred in 5% of patients: 1 non-fatal intracranial bleeding, 2 GI, and 1 vaginal bleeding. Similar results were found in a European cohort of 36 patients with Child A and B cirrhosis (22 with PVT) treated with rivaroxaban (83%), dabigatran (11%), and apixaban (6%). After a median follow-up of 15 months, 1 major bleeding (lower GI) and 4 minor bleedings (portal hypertensive gastropathy, lower GI, post bend ligation) were reported [50]. A recent, multicenter retrospective study evaluated safety of DOACs in 123 patients with cirrhosis/vascular liver diseases treated with DOACs vs. 58 controls treated with LMWH/VKA [99]. Rate of major bleeding was higher in Child B/C patients vs. Child A; however, no significant difference was found between DOAC and LMWH/VKA groups (28.6% vs. 19.0%, respectively; $p = 0.162$) [99].

A recent Egyptian RCT evaluated safety and efficacy of DOACs in patients with cirrhosis and PVT [98]. The investigators randomized 80 patients with Child A or B HCV-related cirrhosis complicated by acute PVT to rivaroxaban (low dosage, 10 mg daily) vs. VKA (monitored by INR). Interestingly, despite the relatively low dosage of rivaroxaban, recanalization of portal vein was obtained in 85% of cases vs. 45% of patients treated with VKA. Not only rivaroxaban was effective in treating PVT, but it was also safe, and rate of bleeding was higher in warfarin (43%) vs. rivaroxaban (no episode of bleeding).

Few cases of probable rivaroxaban-induced liver injury have been reported [101]. Most patients showed transient elevation of serum transaminases and bilirubin which spontaneously resolved after rivaroxaban discontinuation. However, this underlines the need for further data on pharmacovigilance in this setting.

In conclusion, although preliminary and mostly retrospective, these data suggest that DOACs in cirrhosis may be efficient and safe in patients belonging to Child A class. Data regarding Child B are few and DOACs should be used with caution in these patients. In Child C, DOACs should be considered on a case-by-case basis. There is no evidence to suggest any particular DOAC for patients with Child A cirrhosis. Based on pharmacodynamics properties and a favorable drug-induced liver injury profile, it appears that apixaban may be the preferred DOAC in Child B patients. Further prospective studies are awaited to assess the risk/benefit ratio of individual DOACs in cirrhosis, particularly in decompensated patients.

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