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Direct oral anticoagulants in cirrhosis: Rationale and current evidence

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Summary

Cirrhosis is a major health concern worldwide with a complex pathophysiology affecting various biological systems, including all aspects of haemostasis. Bleeding risk is mainly driven by portal hypertension, but in end-stage liver disease it is further increased by alterations in haemostatic components, including platelet function, coagulation, and fibrinolysis. Concurrently, patients with cirrhosis are prone to venous thromboembolic events (VTE) because of the altered haemostatic balance, in particular an increase in thrombin generation. In patients with cirrhosis, vitamin K antagonists (VKA) and low molecular weight heparins (LMWH) are currently the standard of care for VTE prevention, with VKA also being standard of care for stroke prevention in those with atrial fibrillation. However, direct oral anticoagulants (DOAC) could have specific advantages in this patient population. Clinical experience suggests that DOAC are a safe and possibly more effective alternative to traditional anticoagulants for the treatment of VTE in patients with compensated cirrhosis. In addition, emerging data suggest that primary prophylactic treatment with anticoagulants may improve clinical outcomes in patients with cirrhosis by reducing the risk of hepatic decompensation. The selection of the most appropriate DOAC remains to be clarified. This review focuses on the rationale for the use of DOAC in patients with cirrhosis, the specific effects of the different DOAC (as assessed by *in vitro* and *in vivo* pharmacokinetic and pharmacodynamic studies), as well as clinical outcomes in patients with cirrhosis on DOAC.

Introduction

Cirrhosis has a complex pathophysiology, affects various biological systems and is associated with opposing haemostatic alterations in all its components, leading to an unstable balance between prothrombotic (*e.g.*, increased von Willebrand factor and factor VIII, and decreased ADAMTS13, natural anticoagulants, and clot permeability) and pro-haemorrhagic alterations (*e.g.*, decreased coagulation factors with the exception of factor VIII, thrombocytopenia, and increased fibrinolysis).[1,2]

For many years, patients with cirrhosis were considered "auto-anticoagulated" due to misinterpretation of prolonged coagulation time (*i.e.*, prothrombin time [PT] and activated partial thromboplastin time [aPTT]). Both PT and aPTT are sensitive to a decrease in coagulation factors, whereas neither is influenced by a decrease in natural anticoagulants.[3] However, from a haemostatic point of view, over the last decade there has been increasing evidence of rebalanced haemostasis in patients with cirrhosis.[2,4–13] Furthermore, *ex vivo* assays demonstrate increased thrombin generation (TG) and reduced inhibition of endogenous thrombin potential (ETP) in the presence of thrombomodulin (which initiates the anticoagulant protein C pathway), revealing a procoagulant profile in platelet-poor plasma.[14–16] Of note, these observations are beginning to be challanged by a recent study which examined TG in the whole blood of patients with decompensated cirrhosis.[12]

Additionally, clinical studies have shown an increase in venous thromboembolic events (VTE), especially splanchnic thromboses and portal vein thromboses (PVT), the risk of which is increased in more advanced stages of cirrhosis.[4,17,18] Therefore, extended anticoagulation may be indicated for secondary and, according to growing evidence, even primary prevention of VTE in patients with cirrhosis.[19,20]

Low molecular weight heparins (LMWH) and vitamin K antagonists (VKA) have been the standard of care for anticoagulation in patients with cirrhosis despite their indirect action on coagulation factors and relatively unpredictable anticoagulant effect in this population. Direct oral anticoagulants (DOAC), both those targeting activated factor X (FXa) (apixaban, rivaroxaban, edoxaban) and activated factor II (FIIa) (dabigatran), have not been established in patients with cirrhosis. Few data on the efficacy and safety of DOAC exist in this population because patients with cirrhosis have generally been excluded from randomised-controlled trials (RCT). Nevertheless, a retrospective study,[21] as well as several systematic reviews and meta-analyses,[22–27] suggest that the use of DOAC in cirrhosis is a safe and effective alternative to traditional anticoagulant drugs.

This review aims to summarise the current evidence on anticoagulant drugs in cirrhosis, focusing on DOAC. An overview of the rationale for anticoagulation in cirrhosis is provided,

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Keypoints

- Cirrhosis can be associated with a procoagulant state, leading to thrombotic complications (mainly portal vein thrombosis).
- In patients with cirrhosis, anticoagulation appears to not only reduce the risk of venous thromboembolic events and stroke (in case of atrial fibrillation), but also to reduce the risk of hepatic decompensation and improve survival.
- Emerging data suggest that direct oral anticoagulants may be safer and more effective than vitamin K antagonists and low molecular weight heparins in patients with cirrhosis.
- The pharmacokinetics and pharmacodynamics of direct oral anticoagulants in patients with cirrhosis differ from those in individuals without cirrhosis.
- Based on pharmacokinetic and pharmacodynamic data, apixaban and edoxaban may have a particularly compelling pharmacological profile in patients with cirrhosis.

followed by a discussion of the specific advantages and disadvantages of traditional anticoagulants. We then highlight the rationale for the use of DOAC in cirrhosis by discussing the specific effect of each DOAC as assessed by *in vitro* and *in vivo* studies and by addressing clinical outcomes in patients with cirrhosis.

Rationale for anticoagulation in patients with cirrhosis

From a haematological point of view, cirrhosis is a complex condition: portal hypertension and haemostatic alterations can predispose to both haemorrhage and thrombosis.[4,17,18,28–33]

Haemorrhagic events, most commonly variceal bleeding, occur at an incidence of about 5% per year[34,35] and are generally due to increased portal pressure rather than coagulation imbalance. Administration of coagulation factors or platelets does not improve outcomes,[36,37] unlike the vasopressin analogue terlipressin[38] or non-selective beta-blockers.[39–41] Unrelated to portal hypertension, some forms of bleeding, such as intracranial haemorrhage (hazard ratio of 1.4-1.5)[30] and subdural hematomas (hazard ratio of 2.6-3.1),[31] occur more frequently in patients with cirrhosis or may be more severe (*e.g.*, ulcers, muscle hematoma).[28–31] Finally, the periprocedural bleeding risk in patients with cirrhosis deserves consideration.[36]

Some thrombotic complications are the consequence of a procoagulant state, as reflected by, for example, an increase in factor VIII and a decrease in natural anticoagulants, such as protein C, protein S, and antithrombin.[1] Prolonged coagulation times (PT and aPTT) reflect only the decreased level of coagulation factors and not necessarily the bleeding risk since these assays are insensitive to the reduced level of physiological anticoagulants.[3] There is increasing evidence that plasma from patients with advanced liver disease has a procoagulant profile.[2–4,6,8,42,43] Moreover, epidemiological data suggest that the risk of deep vein thrombosis and pulmonary embolism is significantly increased in patients with cirrhosis (hazard ratio of 2.34 according to a prospective cohort study[32] or an odds ratio of 2.04 according to a systematic review and meta-analysis[4]). Additionally, the 1-year incidence of PVT was shown to be higher in patients with cirrhosis compared to the general population[44,45] (4,800/100,000 in patients with cirrhosis *vs*. 0.7/100,000 in the general population), although the incidence of PVT in the general population is probably underestimated due to the absence of active screening. Of note, PVT can also be a direct consequence of portal hypertension in addition to haemostatic alterations.[33,46,47]

VTE and more particularly PVT are common complications in patients with cirrhosis and represent classic indications for anticoagulation. In addition, patients with cirrhosis are at greater risk of developing atrial fibrillation.[48] Anticoagulation is recommended for the following indications: treatment of VTE, secondary prevention of VTE, primary prevention of thromboembolic events in patients with atrial fibrillation or in patients undergoing hip or knee arthroplasty.[49–53] The recent individual patient data (IPD) meta-analysis IMPORTAL based on moderate-quality data has shown that, compared with the absence of anticoagulation (n = 295), traditional anticoagulation (LMWH or VKA; n = 205) could reduce all-cause and liver-related mortality in patients with cirrhosis and PVT (hazard ratio of 0.59).[54] Interestingly, the improvement in prognosis was independent of severity and re-canalisation of PVT, although this study is limited by the heterogeneity of the definition of location, severity, and re-canalisation of PVT in the studies included. Nevertheless, bias and confounding events are minimised by the method (*i.e.* IPD) and adjustment for confounders.

Potential new indications for primary prophylactic anticoagulation in patients with cirrhosis have been suggested by Villa *et al.*.[19] These authors performed a non-blinded, single-centre RCT in 70 outpatients with Child-Turcotte-Pugh (CTP) B7–C10 cirrhosis and showed a significant reduction in mortality, liver decompensation (particularly ascites), and PVT in patients randomised to receive a prophylactic dose of enoxaparin compared to controls. Of note, the reduction in PVT alone could not explain the reduction in liver decompensation and the increase in survival. However, this study was not designed to investigate a pathogenic mechanism. A recent double-blind randomised placebo-controlled trial[55] (discussed below) has also shown possible benefits of prophylactic anticoagulation with rivaroxaban.

Given the improved prognosis observed with anticoagulation independent of PVT re-canalisation according to these studies,[19,55] other rational targets for anticoagulant treatment are conceivable, such as the prevention of small-vessel thrombosis and secondary hepatic fibrosis.[56,57] This is because liver damage is the result of chronic inflammation leading to complex parenchymal architectural distortion via micro-thromboses in the intrahepatic (sinusoidal) circulation, death of hepatocytes, and their replacement by fibrosis.

Accordingly, in rat models, enoxaparin and rivaroxaban have been shown to reduce portal pressure, hepatic stellate cell activation, and fibrin deposits in the liver parenchyma.[58,59] Extrahepatic micro-thrombotic events in the colonic circulation of patients with cirrhosis have also been described as a cause of enterocyte damage, ischaemic complications, and bacterial translocation, possibly affecting prognosis.[19,56] Moreover, single studies have shown that haemostatic parameters (factor VIII/protein C ratio, platelet aggregability) are independent prognostic biomarkers of hepatic events, such as liver decompensation, acute-on-chronic liver failure and death.[60,61] Despite these observations, primary anticoagulation has not yet been established for these indications in patients with cirrhosis.

Advantages and disadvantages of traditional anticoagulants in patients with cirrhosis

Vitamin K antagonists

VKA target vitamin K-dependent coagulation factors (II, VII, IX, X) and natural anticoagulants (protein C/protein S). VKA are known to have several food and drug interactions as well as a narrow therapeutic window requiring monitoring despite the advantage of oral administration. In cirrhosis, the international normalised ratio (INR) may already be increased at baseline,[62,63] reflecting reduced hepatic synthesis of coagulation factors, including non-vitamin K-dependent factor V, which hampers VKA monitoring. In fact, INR depends on all coagulation factors that determine the prothrombin time (factor VII, X, V, II, I), from which INR is calculated, and therefore reflects both the severity of liver dysfunction and the effect of VKA.

Additionally, the use of VKA impacts the calculation of various scores, particularly the model for end-stage liver disease (MELD) score.[64] Both VKA and DOAC may lead to overestimation of liver disease severity by inflating the MELD score, as they increase INR values.[65] To adjust for INR alterations by anticoagulant treatment, MELD-XI (MELD excluding INR) was developed and was demonstrated to be almost as accurate as MELD in predicting short-term survival in patients with cirrhosis.[66]

Low molecular weight heparins

The main anticoagulant action of LMWH is indirect because they increase antithrombin inhibitory activity on activated serine proteases, especially FXa. A significant disadvantage of LMWH is the discomfort associated with their once- to twice-daily subcutaneous administration. For decades, LMWH have been the drug of choice to treat VTE complications in cirrhosis, potentially followed by a switch to VKA. However, the anticoagulant effect of these molecules is difficult to predict in patients with cirrhosis. A decreased anticoagulant potential may be expected because the biological activity of LMWH depends on antithrombin, which is variably reduced[2] in the context of compromised hepatic protein synthesis. However, this hypothesis has been debated since Senzolo *et al.*[67] found a paradoxically increased anticoagulant response to LMWH in cirrhosis. This and other studies have demonstrated that there is a risk of overdosing LMWH in this population, because lower than expected anti-Xa activity for the dose/body weight ratio has been observed.[67–69] The enhanced antithrombotic potential of LMWH in cirrhosis could be mediated by the antithrombin-independent anticoagulant action of mobilised tissue factor pathway inhibitor, a natural anticoagulant factor that is stored mainly in the endothelium and inhibits tissue factor-bound activated factor VII.[70] With regard to the risk of overdose in patients with decompensated cirrhosis, overestimation of body weight as a result of fluid accumulation (*e.g.*, ascites), and impaired renal elimination of LMWH[71] as a result of acute kidney failure (*e.g.*, hepato-renal syndrome) should also be taken into account. Nonetheless, LMWH are still a drug of choice in cirrhosis because they are well known, reasonably efficient and safe, and close monitoring of anti-Xa activity is usually not necessary.

Direct oral anticoagulants and cirrhosis

Rationale for the use of direct oral anticoagulants in patients with cirrhosis

In the general population, DOAC have revolutionised the prevention and treatment of VTE, as well as the primary and secondary prevention of ischaemic stroke and systemic embolism in patients with atrial fibrillation. DOAC are simpler to manage than VKA and LMWH because they are administered orally, doses are fixed, therapeutic drug monitoring is generally not required, and fewer drug and food interactions have been reported.[49–52] Furthermore, DOAC have a better safety profile than traditional anticoagulants and are associated with a markedly reduced risk of intracranial haemorrhage.[72–75] Unfortunately, specific populations such as patients with CTP-B and CTP-C cirrhosis are often excluded from clinical trials because DOAC undergo hepatic metabolism to varying degrees, and potential drug accumulation may lead to bleeding complications. Nevertheless, DOAC are also compelling anticoagulant drugs for patients with cirrhosis because of their direct mode of action and oral intake. Additionally, retrospective studies suggest that DOAC are not inferior to traditional anticoagulant drugs in terms of safety and efficacy, and may even be a safer and more effective alternative to VKA and LMWH.[22–27]

Direct oral anticoagulants – pharmacokinetic and pharmacodynamic considerations

Pharmacokinetics of direct oral anticoagulants in cirrhosis

The systemic absorption of DOAC in patients with cirrhosis seems unimpaired because of an insignificant first-pass effect.[76] Nevertheless, higher DOAC plasma concentrations in this population may be expected for several reasons. Liver dysfunction is associated with lower albumin levels and can cause an increase of the unbound, active fraction of high plasma protein binding DOAC like apixaban and rivaroxaban (Table 1).[76] Decreased clearance of DOAC may be expected, especially those metabolised by cytochromes P450 (CYP450), such as direct inhibitors of FXa (rivaroxaban, apixaban and edoxaban).[76] Direct inhibitors of FXa are mostly metabolised by CYP3A4 and to a lesser extent by other CYP450 enzymes (Table 1). However, the impact of the CYP450 system is difficult to predict because the sensitivity of each cytochrome is specific to each individual and may be further altered according to the stage of cirrhosis.[77] Additionally, higher plasma

Table 1. General and cirrhosis-specific pharmacokinetic considerations of DOAC.

	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Target	Activated factor X	Activated factor X	Activated factor X	Activated factor II
Application	Oral	Oral	Oral	Oral
Pro-drug	No	No	No	Yes, converted in plasma and liver in its active form
Food interaction	Yes, food intake is required to improve bioavailability of RVX 15 mg and 20 mg	No	No	No
Bioavailability (%)	66 (without food) 80-100 (with food) for RVX 15 and 20 mg	50	62	6-7
Cmax (h)	2-4	3-4	1-2	0.5-2
Half-life (h)	5-9	12	10-14	12-14
Volume of distribution (L)	50	21	107	60-70
Protein binding (%)	92-95	87	55	35
Metabolism via CYP450 (%)	66	30	<10	None
Type of CYP450	CYP3A4, CYP2J2	CYP3A4/5 (major implication) CYP1A2 (minor) CYP2C8/2C9/2C19/2J2 (minor)	CYP3A4/5	
Elimination pathways (%)				
Hepatobiliary/faecal excretion	33[1]	75[2]	50	20 (conjugated with glucuronic acid)
Renal	66 (36% unchanged and 30% as metabolites)	25 (mostly unchanged)	50 (mostly unchanged)	80 (mostly unchanged)
P-gp substrate	Yes	Yes	Yes	Yes
Therapeutic doses:				
Standard	20 mg	2x 5 mg	60 mg	2x 150 mg
Adjusted/reduced	15 mg	2x 2.5 mg	30 mg	2x 110 mg
Therapeutic dose adaptation according to renal function				
CrCl >50 ml/min	Standard dose	Standard dose	Standard dose	Standard dose
CrCl 50-30 ml/min	Adjusted dose	Standard dose	Adjusted dose	Adjusted dose
CrCl 30-15 ml/min	Adjusted dose	Adjusted dose	Adjusted dose	Avoid
CrCl <15 ml/min	Avoid	Adjusted dose or avoid	Avoid	Avoid
AUC in cirrhosis:				
CTP-A	+15%[2]	+3%[3]	-4.2%[4]	No data
CTP-B	+227%[2]	+9%[3]	-4.8%[4]	-6%[5]
CTP-C	No data	No data	No data	No data
Drug administration recommendations according to severity of cirrhosis:				
CTP-A	Standard dose	Standard dose	Standard dose	Standard dose
CTP-B	Avoid	Use with caution	Use with caution	Use with caution
CTP-C	Avoid	Avoid	Avoid	Avoid

AUC, area under the curve; CrCl, creatinine clearance according to Cockcroft-Gault; CTP, Child-Turcotte-Pugh; CYP450, cytochrome P450; DOAC, direct oral anticoagulants; P-gp, P-glycoprotein; RVX, rivaroxaban.
[1]Proportion extrapolated from the renal clearance (66%); hepatic metabolism seems to be implicated in two-thirds of the elimination (66% of the study dose was recovered as metabolites), but renal elimination is also implicated to a similar extent (33% of the study dose was recovered unchanged in urine and 33% as inactive metabolites) (51, 76, 78, 97, 98). [2] Proportion extrapolated from the renal clearance (25%); the exact contribution of each elimination pathway is not known: biliary excretion exerts a minor role (3%), hepatic metabolism seems to be implicated in one-third of the elimination (30% of the study dose was recovered as metabolites), whereas direct intestinal excretion seems to be a major pathway (56% of the study dose recovered in faeces) (95).[2](82)[3](83)[4](81)[5](84), (49–52, 73, 80, 92, 96, 97, 100).

concentrations of DOAC may be considered if biliary excretion is reduced. The direct thrombin inhibitor dabigatran is partly bio-converted to the active compound by the liver.[76] Thus, decreased plasma concentrations of dabigatran may be expected with liver impairment.

Of note, apixaban is mostly eliminated via the non-renal route (75% through hepatobiliary/faecal excretion), approximately one-third of rivaroxaban is excreted unchanged in the urine (with the remaining two-thirds excreted as inactive metabolites both renally and via the faecal route),[78] and edoxaban is eliminated to a similar extent via renal and non-renal routes (50%-50%), whereas dabigatran primarily undergoes renal elimination (only 20% hepatobiliary/faecal excretion).[49–52,76] Impaired renal excretion needs to be considered in patients with cirrhosis taking drugs with predominant renal elimination such as dabigatran.[76,79] Deterioration of renal clearance may occur, for example, in the context of hepatorenal syndrome. Thus, dose adaptation to kidney function (and/or switch to alternative DOAC) should be considered, particularly when creatinine clearance is less than 50 ml/min (Table 1).[80]

Four pharmacokinetic studies[81–84] assessed the exposure (area under the curve [AUC]) of each DOAC after a single dose and demonstrated discordant effects in patients with CTP-A and CTP-B cirrhosis. Exposure (AUC) to apixaban and rivaroxaban increased with increasing cirrhosis severity, while the reverse was observed for edoxaban and dabigatran (Table 1). Of note, the AUC of rivaroxaban was significantly increased (+227%) after a single administration in patients with CTP-B cirrhosis, meaning that an enhanced and significant accumulation may be expected in patients with advanced cirrhosis receiving repeated doses of rivaroxaban. However, these four studies have several limitations, such as small sample sizes, single dose administration (preventing assessment of the accumulation risk), lower doses than those used in clinical practice to achieve therapeutic anticoagulation, and the exclusion of patients with CTP-C cirrhosis.

Drug-drug interactions (DDI) must be considered when administering DOACs, as other molecules are frequently prescribed to patients with cirrhosis. However, the available literature is inconclusive on this subject and conflicting information may be found. Clinicians should be aware of possible DDI and actively check for them with different online databases such as “Lexicomp”[85] and “Epocrates”.[86] “DDI & cirrhosis predictor”[87] is also an interesting tool to evaluate the AUC of drugs in patients with cirrhosis according to their CTP score. Pharmacokinetic monitoring of DOAC treatment may be useful in some complex cases by measuring DOAC trough concentrations to exclude accumulation.[88]

Pharmacodynamics of direct oral anticoagulants in cirrhosis

In vitro *data.* The *in vitro* anticoagulant effect appears to differ among DOAC (Table 2). Lisman *et al.*[89] analysed the *in vitro* effect of several pro- and anticoagulant agents including rivaroxaban, dabigatran and LMWH in patients with compensated cirrhosis (n = 18), acute decompensation (n = 18), acute-on-chronic liver failure (n = 10) and healthy controls. TG parameters were measured after the addition of rivaroxaban 25 ng/ml, dabigatran 300 ng/ml and LMWH 0.2 U/ml to plasma samples from patients and controls. Compared to controls, an increase in the anticoagulant potency of LMWH and an extreme increase in the anticoagulant potency of dabigatran were demonstrated. Dabigatran is an attractive option in cirrhosis because of its low hepatic metabolism; the thrombin inhibitor also has a potent *in vitro* anticoagulant effect in patients with cirrhosis, even in CTP-A cirrhosis, which seems to increase with the severity of liver disease. Further investigations are required to identify if this potent *in vitro* anticoagulant effect of dabigatran is also observed *in vivo* and may justify a dose reduction. Nevertheless, this finding should be balanced with the possible decreased plasma level of dabigatran induced by the lower conversion by the liver of the pro-drug dabigatran etexilate into active dabigatran in cirrhosis.[76] In contrast, rivaroxaban appears to be less effective with the increase of cirrhosis severity. Thus, higher blood concentrations may be required to achieve the same effect. These observations are supported by Potze *et al.*,[90] who showed that the impact of rivaroxaban on two TG parameters (*i.e.*, peak height and ETP) was less pronounced in plasma from patients with CTP-C cirrhosis compared to controls. This group also assessed the *in vitro* anticoagulant effect of apixaban 25 ng/ml added to plasma samples of 14 patients with cirrhosis (9 patients with CTP-B cirrhosis and 5 patients with CTP-C cirrhosis).[91] TG parameters were measured and showed decreased anticoagulant potency of apixaban in patients with CTP-B and CTP-C cirrhosis. Of note, the concentrations used by Lisman *et al.* and Potze *et al.* for rivaroxaban (25 ng/ml; 50 ng/ml),[89–91] apixaban (25 ng/ml)[91] and LMWH (0.2 U/ml)[89,90] reflect low-intensity anticoagulation, whereas the concentration of dabigatran (300 ng/ml)[89,90] represents high-intensity anticoagulation.

In vivo *considerations.* Edoxaban is of interest in patients with cirrhosis despite significant hepatobiliary clearance (>50% eliminated by the liver[50,76,92,93] (Table1)). Its anticoagulant potency seems to decrease with the severity of cirrhosis.[81,94] Only a prospective interventional study investigated the *in vivo* and *ex vivo* anticoagulant effect of edoxaban in patients with CTP-A cirrhosis (Table 2).[94] The authors analysed the administration of edoxaban 60 mg once daily for 7 days in 16 patients with cirrhosis (15 CTP-A, 1 CTP-B cirrhosis) compared to controls. Blood samples were drawn at peak levels at days 1, 3 and 7, and TG parameters, D-dimers and anti-Xa activity (reflecting edoxaban plasma concentration) were assessed. ETP was significantly higher in patients with cirrhosis compared to controls at baseline and on days 1, 3, and 7. While anti-Xa activity remained constant over time in both groups, D-dimer levels remained unchanged in patients with cirrhosis but decreased significantly in controls. These results show that even if plasma levels of edoxaban are similar in patients with CTP-A cirrhosis and controls, *in vivo* and *ex vivo* anticoagulant effects of edoxaban are less pronounced in patients with CTP-A cirrhosis. Based on these observations, the authors hypothesised that a dose reduction of edoxaban may not be necessary in this population and may lead to under-treatment.

Apixaban is mostly eliminated by hepatobiliary/faecal excretion (about 75%)[49,76,95,96] (Table 1). Apixaban appears to have a decreased anticoagulant effect in patients with CTP-B or CTP-C cirrhosis.[91] A pharmacokinetic study also showed a slightly increased AUC after a single dose.[83] These observations suggest that apixaban may be safe and effective with a favourable profile in patients with cirrhosis (Table 1).

Rivaroxaban undergoes mostly hepatobiliary/faecal excretion (about 66%)[51,76,97,98] (Table 1). A pharmacokinetic study found a markedly increased AUC in patients with CTP-B

Table 2. *In vitro* and *in vivo* pharmacodynamic data of DOAC in cirrhosis.

Study	Characteristics	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
***In vitro* studies**					
Lisman *et al.*[89]	Spiked concentration	**25 ng/ml**	*Not investigated*	*Not investigated*	**300 ng/ml**
	Population	CC (n = 18), AD (n = 18), ACLF (n = 10), HD (n = 30)			CC (n = 18), AD (n = 18), ACLF (n = 10), HD (n = 30)
	Results	Reduction of ETP, PH and VI (HD>CC>ACLF>AD) Prolonged LT (ACLF>CC>AD>HD)			Reduction of ETP, PH and VI (AD>CC>HD); no TG produced in ACLF Prolonged LT (HD>AD>CC); no TG produced in ACLF
	Conclusion	**RVX** appears **less effective** in decreasing TG in cirrhosis compared to HD.			**DAB** appears to exert a **stronger anticoagulant potency** in cirrhosis compared to HD.
Potze *et al.*[90]	Spiked concentration	**25 ng/ml**	*Not investigated*	*Not investigated*	**300 ng/ml**
	Population	CTP-A cirrhosis (n = 10) CTP-B cirrhosis (n = 10), CTP-C cirrhosis (n = 10), HD (n = 30)			CTP-A cirrhosis (n = 10) CTP-B cirrhosis (n = 10), CTP-C cirrhosis (n = 10), HD (n = 30)
	Results	Reduction of ETP (CTP-B>HD>CTP-A>CTP-C) Reduction of PH (HD>CTP-A>CTP-B>CTP-C) Reduction of VI (CTP-A>CTP-B>CTP-C>HD) Prolonged LT (CTP-B>CTP-A>HD>CTP-C)			Reduction of ETP, PH, VI (CTP-C>CTP-B>CTP-A>HD) Prolonged LT (CTP-A>HD>CTP-B>CTP-C)
	Conclusion	**RVX** appears **less effective** in decreasing TG in cirrhosis and this decreased effect seems to be **proportional to cirrhosis severity.**			**DAB** appears to exert a **stronger anticoagulant potency** in cirrhosis compared to HD. The enhanced effect seems to be **proportional to cirrhosis severity.**
Potze *et al.*[91]	Spiked concentration	**50 ng/ml**	**25 ng/ml**	*Not investigated*	*Not investigated*
	Population	CTP-B cirrhosis (n = 9), CTP-C cirrhosis (n = 5), HD (n = 11)	CTP-B cirrhosis (n = 9), CTP-C cirrhosis (n = 5), HD (n = 11)		
	Results	Reduction of "total TG" (cirrhosis: -30%; HD: -55%)	Reduction of "total TG" (cirrhosis: -32%; HD: -51%)		
	Conclusion	**RVX appears less effective** in decreasing TG in cirrhosis compared to HD.	**APX appears less effective** in decreasing TG in cirrhosis compared to HD.		
***In vivo* study**					
Bos *et al.*[94]	Study dose	*Not investigated*	*Not investigated*	**60 mg once a day**	*Not investigated*
	Design			Prospective clinical trial	
	Population			CTP-A cirrhosis (n = 15), CTP-B cirrhosis (n = 1), HD (n = 16)	
	Duration of treatment			7 days	
	Results			Reduction of ETP (HD>cirrhosis) Reduction of D-dimers in HD (not in cirrhosis) Anti-Xa levels remain similar between HD and cirrhosis	
	Conclusion			**EDX** reduced *ex vivo* and *in vivo* haemostatic potential **less efficiently in cirrhosis** compared with HD.	

ACLF, acute-on-chronic liver failure; AD, acutely decompensated cirrhosis; APX, apixaban; CC, compensated cirrhosis; CTP, Child-Turcotte-Pugh; DAB, dabigatran; DOACs, direct oral anticoagulants; EDX, edoxaban; ETP, endogenous thrombin potential; HD, healthy donor; LT, lag time; PH, peak height; RVX, rivaroxaban; TG, thrombin generation; VI, velocity index.

cirrhosis after a single dose, which may lead to over-anticoagulation.[82] Nevertheless, *in vitro* studies identified a decreased anticoagulant effect of rivaroxaban in plasma from patients with cirrhosis.[89–91]

Dabigatran has an attractive profile because of its primarily non-hepatic elimination[52,79,99,100] (Table 1). However, dabigatran demonstrates a more potent *in vitro* anticoagulant effect in patients with cirrhosis than in controls, even in those with CTP-A cirrhosis.[89,90]

In summary, on the sole basis of the limited published pharmacokinetic and pharmacodynamic data on patients with cirrhosis, we can only formulate hypotheses regarding suitability and dose adaptations of DOAC in this population. According to these data, apixaban and edoxaban appear to be appropriate for patients with cirrhosis, including CTP-B cirrhosis. These two DOAC should therefore be further evaluated in prospective clinical trials. We consider that in addition to the measurement of DOAC plasma concentrations at trough level, the assessment of pharmacodynamic endpoints, such as changes of *in vivo* TG markers (*e.g.*, prothrombin fragments 1 and 2, thrombin-antithrombin complexes, D-dimers)[101] and relative modulation of *ex vivo* TG parameters (*e.g.*, lag time, time to peak, peak height, velocity index) are necessary to evaluate the anticoagulant potential of DOAC in patients with cirrhosis (Pereira Portela C *et al.* Manuscript submitted).

Clinical outcomes of patients with cirrhosis on direct oral anticoagulants

Currently, DOAC are only indicated in patients with CTP-A (all four) and CTP-B cirrhosis (except rivaroxaban) for the primary prevention of systemic embolism in atrial fibrillation or VTE in hip or knee replacement surgery and for treatment and secondary prevention of VTE. CTP-C cirrhosis is a common contraindication for all DOAC.[49–52]

Venous thromboembolism

Meta-analyses and systematic reviews support the use of DOAC in patients with cirrhosis to treat VTE including PVT with a profile that is at least as safe and effective as traditional anticoagulants.[24,25,27,102] As a note of caution, these reviews and meta-analyses have the same limitations as the observational studies on which they are based. The most important limitations are small sample size (less than a thousand patients included), selection bias, heterogeneity of the data, different definition of liver disease, lack of systematic stratification based on CTP or HAS-BLED scores, and lack of inclusion of patients with CTP-C cirrhosis or significant renal impairment.

Portal vein thrombosis

Han Ng *et al.*[102] and Koh *et al.*[25] described a significantly increased re-canalisation rate of PVT and a decreased PVT progression rate with DOAC compared to VKA. Similar observations were reported by Nagaoki *et al.*,[21] who investigated 50 patients with PVT (including 17 with hepatocellular carcinoma) initially treated with danaparoid, where one group was switched to edoxaban and the other to warfarin (VKA). However, the dose of VKAs was adjusted to reach an INR of 1.5-2.0 (lower than the usual range of 2.0-3.0) to limit bleeding events in patients with cirrhosis, and there was no overlap between danaparoid and VKA treatment. These considerations may explain the progression of PVT in the VKA-treated group.

Complications of atrial fibrillation

Compared to VKA, DOAC appear to significantly reduce the risk of ischaemic stroke,[23,25,26,53] major bleeding events and gastrointestinal bleeding[23,26,103–105] in patients with cirrhosis and atrial fibrillation. Additionally, a recent small RCT of moderate quality involving 56 patients with CTP-A and CTP-B cirrhosis and atrial fibrillation has shown a significantly lower overall frequency of bleeding events with dabigatran compared to VKA.[106] The choice of anticoagulation in patients with CTP-C cirrhosis remains an open question because only limited data are available on the subject. Small-scale observational studies of fewer than 20 patients with CTP-C cirrhosis found no statistical difference in efficacy and safety between DOAC and traditional anticoagulants for treating VTE and preventing systemic embolism in case of atrial fibrillation.[107,108]

Overall, high-quality studies in patients with cirrhosis are still needed to evaluate whether DOAC, especially apixaban and edoxaban, are safer and possibly more effective than VKA or LMWH for standard indications.

Expanding the spectrum of indications

New indications for anticoagulation may be considered in the future to improve survival of patients with cirrhosis, more specifically in the primary prevention of VTE and possibly in the prevention of liver decompensation. A recent multicentre, double-blind, randomised placebo-controlled trial by Puente-Sanchez *et al.* (CIRROXABAN trial; NCT02643212)[55] investigated the effect of a prophylactic dose of rivaroxaban (10 mg daily) *vs*. placebo for 24 months on survival, progression of cirrhosis and the occurrence of PVT in 90 patients with CTP-B cirrhosis. To date, the results of this trial have only been published in abstract form. The investigators found that a prophylactic dose of rivaroxaban improves decompensation-free and transplant-free survival of patients with cirrhosis, with a non-significant increase in non-portal hypertension-related bleeding complications. However, the statistical power of this study has been limited because of the challenges with the recruitment of patients. Further evidence is expected with the publication of the trial.

Conclusions

DOAC are promising drugs for the anticoagulation of patients with cirrhosis. This complex and fragile population has been recognised to be at increased risk of both bleeding and thrombotic complications. Patients with cirrhosis may benefit from secondary or even primary prevention of VTE with DOAC in specific clinical settings adapted to renal function (Table 1). While the paucity of prospective data does not yet justify a change in clinical practice, recent meta-analyses and systematic reviews suggest that DOAC may be a safe and effective alternative to traditional anticoagulants (VKA, LMWH) in patients with cirrhosis. Moreover, anticoagulation with DOAC seems to provide additional clinical benefits in patients with cirrhosis by reducing liver decompensation without increasing major bleeding risk. Altogether, direct FXa inhibitors appear to

have an acceptable profile for patients with CTP-A cirrhosis. In patients with CTP-B cirrhosis, apixaban and edoxaban appear to be appropriate anticoagulants. Whether rivaroxaban is suitable in patients with CTP-B cirrhosis needs to be further investigated because *in vitro* data demonstrate an increased exposure, but preliminary results of the CIRROXABAN trial[55] suggest that a prophylactic dose of rivaroxaban may be safe. The data available on dabigatran are insufficient to offer any recommendation. Further prospective randomised studies are warranted to investigate and confirm the effect of the various DOAC on clinical outcomes of patients with various stages of cirrhosis.

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Abbreviations

aPTT, activated partial thromboplastin time; AUC, area under the curve; CTP, Child-Turcotte-Pugh; CYP450, cytochrome P450; DDIs, drug-drug interactions; DOAC, direct oral anticoagulants; ETP, endogenous thrombin potential; INR, international normalised ratio; LMWH, low molecular weight heparins; MELD, model for end-stage liver disease; PT, prothrombin time; PVT, portal vein thrombosis; RCT, randomised-controlled trials; TG, thrombin generation; VKA, vitamin K antagonists; VTE, venous thromboembolic events.

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Conflicts of interest

The authors declare no conflict of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conceptualisation, C.P.P., L.A.; literature review and tables, C.P.P, L.G.; writing-original draft preparation/review and editing, C.P.P, L.G.; proofreading/critical thinking, M.Z., M.F., D.M., D.B.C, A.A., L.V., A.D.G, G.S, L.A.; supervision, L.A. All authors have read and agreed to the published version of the manuscript.

Supplementary data

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