Review

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Established and new-generation antithrombotic drugs in patients with cirrhosis – Possibilities and caveats

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Summary

Until recently, it was widely accepted that patients with cirrhosis have a bleeding tendency related to the changes in the hemostatic system that occur as a consequence of the disease. However, it has now been well established that patients with cirrhosis are at risk for both bleeding and thrombotic complications. These thrombotic complications include portal vein thrombosis, deep vein thrombosis and pulmonary embolism, and coronary or cerebrovascular infarctions. Antithrombotic drugs to prevent or treat thrombotic complications in patients with cirrhosis have been used only minimally in the past due to the perceived bleeding risk. As the thrombotic complications and the necessity of antithrombotic treatment in these patients are increasingly recognized, the use of antithrombotic drugs in this population is likely increasing. Moreover, given the rising incidence of fatty liver disease and generally longer survival times of patients with chronic liver diseases, it would be reasonable to presume that some of these thrombotic complications may be increasing in incidence over time. In this review, we will outline the indications for antithrombotic treatment in patients with cirrhosis. Furthermore, we will discuss the available antithrombotic drugs and indicate possible applications, advantages, and caveats. Since for many of these drugs very little experience in patients with cirrhosis exists, these data are essential in the design of future clinical and laboratory studies on mechanisms, efficacy, and safety of the various antithrombotic strategies in these patients.

Keywords: Cirrhosis; Thrombosis; Venous thrombosis; Portal vein thrombosis; Arterial thrombosis; Treatment; Anticoagulant drugs.
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Abbreviations: PT, prothrombin time; aPTT, activated partial thromboplastin time; PVT, portal vein thrombosis; LMWH, low molecular weight heparin; DVT, deep vein thrombosis; VKA, vitamin K antagonists; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; HIT, heparin-induced thrombocytopenia; GI, gastrointestinal; INR, international normalized ratio.

Introduction

Cirrhosis is frequently associated with complex changes in the hemostatic system. These changes include thrombocytopenia and platelet function defects, decreased levels of pro- and anticoagulant proteins, and alterations in the fibrinolytic system. The net result of these changes has long been thought to be a bleeding tendency. Indeed, routine diagnostic tests of hemostasis, such as the platelet count, and coagulation tests, such as the prothrombin time (PT) and activated partial thromboplastin time (aPTT), indicate a hypocoagulable state. Clinical experience in patients with liver disease combined with sophisticated laboratory studies of hemostasis has led to the conclusion that despite the major changes in the hemostatic system associated with cirrhosis, the net result is a system that remains in balance due to a commensurate decline in pro- and antihemostatic pathways. This 'rebalanced' hemostatic system in patients with cirrhosis, however, appears much more fragile compared to the hemostatic balance of healthy individuals (Fig. 1). This precarious hemostatic balance explains why patients with cirrhosis may experience bleeding complications as well as thrombotic episodes [1,2].

Until recent years, the common belief was that patients with cirrhosis were protected against thrombotic disease as they were 'auto-anticoagulated' as suggested by prolonged routine tests of hemostasis. Consequently, antithrombotic therapy to prevent or treat thrombotic disease was used minimally. Limited use of antithrombotic drugs is also explained by the perceived bleeding risk. Nowadays, there is increasing recognition of various thrombotic complications that may occur in patients with chronic liver diseases [3–5]. With increasing rates of fatty liver disease and generally longer survival times in patients with chronic liver diseases, it would be reasonable to presume that some of these complications may be increasing in incidence over time. Prevention or treatment of these complications is complex due to many issues including dosing, monitoring, and safety of the available antithrombotic agents. In this review, we will discuss the thrombotic complications that may occur in patients with cirrhosis. Subsequently, we will discuss advantages and disadvantages of currently available antithrombotic drugs that potentially could be used to treat thrombotic complications of patients with liver disease. We would like to stress that there are no established guidelines for treatment or prevention of thrombotic disease in

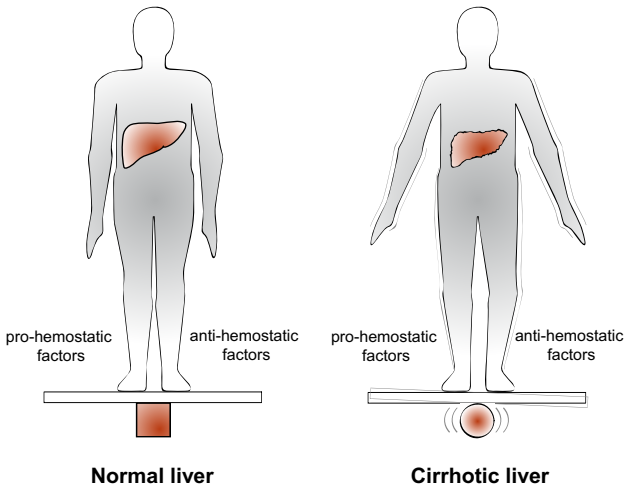

Fig. 1. The hemostatic balance in patients with liver disease as compared to that of healthy individuals. This cartoon depicts the stable hemostatic balance in healthy individuals and shows that although the hemostatic system in patients with liver disease is (re)balanced, the balance is fragile and may easily tip to either a hypo or hypercoagulable status.

patients with liver disease. In addition, there is limited clinical data to support or refute the use of available antithrombotic drugs for the different potential indications. We aim at giving an overview of pros and cons of the available drugs with the aim to provide a rationale for future studies on safety and efficacy of potential antithrombotic strategies for the different indications. In our discussion of the possible antithrombotic drugs, we have limited ourselves to antithrombotic drugs that are recommended for venous and arterial events in the general population in the most current guidelines, and only discuss drugs that are generally available for clinical use.

Thrombotic diseases in patients with cirrhosis

Portal vein thrombosis

A common complication of cirrhosis is development of portal vein thrombosis (PVT), which is associated with clinical deterioration [6]. Furthermore, PVT complicates liver transplant surgery, and may adversely affect outcome after liver transplantation [7]. Although there are no established guidelines for treatment of PVT in a patient with cirrhosis, anticoagulant therapy with low molecular weight heparin (LMWH) or vitamin K antagonists (VKAs) results in recanalisation in a proportion of patients with established PVT [8–11]. There are multiple reasons to assume that successful recanalisation improves clinical outcome. First, an untreated PVT may extend further into the mesenteric/splenic venous system, leading to venous infarction. Second, an untreated PVT may result in accelerated progression of disease as a result of accelerated 'parenchymal extinction' [12]. There is, however, little clinical evidence as to whether recanalisation following anticoagulant therapy indeed improves clinical outcome.

Currently, no strategies to prevent development of PVT are available. Nevertheless, a recent randomized trial demonstrated that a daily prophylactic administration of a prophylactic dose of LMWH prevents PVT in patients with compensated cirrhosis, and in addition appears to delay hepatic decompensation [13].

Although PVT is generally regarded as a deep venous thrombosis, it has not yet been established whether the pathophysiology of the portal vein thrombus indeed resembles the classical venous thrombus (i.e., a fibrin-rich thrombus, as opposed to the platelet-rich thrombus that occurs in systemic arterial thrombosis such as myocardial infarction or stroke). The effect of antiplatelet drugs on PVT has not yet been explored in the non-liver transplant setting, which may be due to the bleeding risk associated with aspirin in patients with esophageal varices [14].

Venous thrombosis

Multiple studies have demonstrated that patients with chronic liver disease are not protected against venous thrombosis (which includes deep vein thrombosis (DVT) and pulmonary embolism), even in the presence of mechanical or pharmacological thromboprophylaxis [15–18]. Some studies indicate that chronic liver disease is in fact a risk factor for venous thrombosis with a more than 2-fold increased risk [15], although not all studies agree [19].

Treatment of venous thrombosis in the general population during immobilization, hospitalization or following major surgery is typically achieved with LMWH followed by VKAs or by novel anticoagulant agents, including oral direct factor Xa and IIa inhibitors [20]. Primary prevention of venous thrombosis in the general population is achieved by LMWH, the heparin-derived synthetic pentasaccharide fondaparinux, low-dose unfractionated heparin, or by oral anti Xa or IIa inhibitors [20]. The oral Xa and IIa inhibitors Rivaroxaban and Dabigatran have been registered for primary prophylaxis after orthopedic surgery. There is mounting evidence that thromboprophylactic treatment is safe in patients with cirrhosis [21] and it would follow that prophylaxis should not be withheld from patients with liver disease even in the presence of abnormal routine tests of coagulation. Indications for thromboprophylaxis include hospitalization and immobilization, surgery, and perhaps also the presence of (hepatocellular) cancer, as cancer in general is a risk factor for venous thrombosis.

Arterial thrombosis

The incidence of arterial thrombotic events, including coronary and cerebrovascular infarctions, was traditionally believed to occur in a lower frequency in patients with cirrhosis as compared to the general population [22–24]. Recent studies, however, have challenged these earlier findings [25–27]. Patients with non-alcoholic fatty liver disease (NAFLD) have been repeatedly shown to have an increased risk for arterial disease, which is in fact the leading cause of death in this group [28]. As the number of patients with NAFLD/non-alcoholic steatohepatitis (NASH) is increasing, the number of patients with both liver and cardiovascular disease will likely increase as well.

For primary prevention of arterial disease in the general population >50 years of age, low dose aspirin therapy may be considered. Antithrombotic therapy and/or secondary prevention of cardiovascular events consist of antiplatelet monotherapy (aspirin or clopidogrel) for patients with established coronary artery disease and dual antiplatelet therapy (aspirin with a P2Y12 receptor blocker) following acute coronary syndromes with

percutaneous coronary intervention and stent placement [20]. Secondary prevention of ischemic stroke consists of single anti-platelet therapy or oral anticoagulant therapy. Secondary prevention of arterial events should presumably not be withheld from patients with cirrhosis, but the risk of bleeding complications may be increased (see below).

Thrombosis as a contributor to progression of disease

Increasing evidence from animal models of chronic or acute liver failure suggests that antithrombotic treatment slows down progression of disease [29–31]. Mechanistic explanations for this phenomenon include formation of microthrombi resulting in local ischemia (referred to as 'parenchymal exctinction') and direct activation of disease-promoting cells by coagulation proteases [12]. Also, patients with cirrhosis and inherited thrombophilia appear to have a faster disease progression [32], whereas disease progression in patients with hemophilia in combination with hepatitis C appears slower [33]. A recent randomized trial demonstrated that a daily prophylactic administration of a prophylactic dose of LMWH to patients with compensated cirrhosis may delay hepatic decompensation [13]. The results of this trial not only indicate that the proposed theory on intrahepatic thrombus formation as a contributor to progression of disease is likely correct, but also suggest that intrahepatic thrombosis is treatable. In addition to this recently published study, a study examining the effect of warfarin anticoagulation on hepatitis C recurrence after liver transplantation has been initiated (Clinicaltrials.gov: NCT00180674), and similar studies in the pre-transplant patient are underway, although the choice of antithrombotic agent is unclear.

Key Points 1

- Anticoagulants have been successfully used to treat PVT in patients with cirrhosis, and a single study showed that anticoagulants are effective in prevention of PVT in patients with cirrhosis
- Patients with cirrhosis are not protected against venous thrombosis.Thromboprophylaxis, for example during hospitalisation, immobilisation or after surgery, should not be witheld, even in the absence of abnormal indices of hemostasis, such as a prolonged PT/INR
- Patients with cirrhosis are not protected against arterial thrombosis, and the incidence of arterial events is even increased in patients with NAFLD/NASH compared to the general population. Patients with cirrhosis and an arterial event will often (if not always) receive antiplatelet therapy which may be associated with a bleeding risk
- Antithrombotic therapy reduces progression of liver diseases in animal models, and a single randomized clinical trial showed that LMWH delays decompensation in patients with compensated cirrhosis
- The best choice of antithrombotic agent as well as safe dosing regimens for all these indications has not yet been established

Pros and cons of different antithrombotic drugs in patients with cirrhosis

Anti-platelet agents

Unlike many anticoagulant drugs, anti-platelet agents do not require laboratory monitoring for dose adjustments, so many of the issues regarding monitoring that are present in the use of anticoagulants in patients with cirrhosis do not apply to anti-platelet agents. Nevertheless, functional tests are sometimes performed to assess anti-platelet drug efficacy, as some patients appear to be resistant against aspirin or Clopidogrel [34]. Despite this, no tests are usually performed to avoid excessive inhibition of platelet function. Tests to detect anti-platelet-resistance in patients with cirrhosis may be complicated by thrombocytopenia and platelet function defects that are already present in the patient with cirrhosis [35]. As laboratory tests of platelet function are frequently abnormal in patients with cirrhosis, it may be challenging to detect efficacy of anti-platelet agents, but the clinical relevance of laboratory evidence of resistance against anti-platelet regimens is unclear.

There is tremendous clinical evidence for the efficacy of aspirin in secondary prevention of arterial disease. The published study with aspirin in patients with cirrhosis, however, is limited. Cirrhosis has been listed as an absolute contraindication for aspirin use due to gastrointestinal (GI) bleeding risk [14,36]. Furthermore, patients with ascites may suffer from acute renal failure, hyponatremia, and diuretic resistance in response to aspirin treatment [37], although these complications are rare at the low doses used for antiplatelet therapies. Nevertheless, the number of patients with cirrhosis that require antiplatelet therapy for secondary prevention of arterial events (e.g., after coronary stenting) is likely increasing over time due to the increasing prevalence of NAFLD/NASH. The currently available evidence suggests that aspirin is relatively safe in terms of bleeding risk in patients with cirrhosis, but without significant varices, after coronary artery stenting [38]. On the other hand, use of aspirin has been associated with an increased risk of a first variceal bleeding in patients with established varices, and therefore, in these patients aspirin is likely contraindicated for primary, and perhaps also for secondary prevention [14].

Inhibitors of the P2Y12 receptor, which block ADP-induced platelet aggregation, have become an integral part of treatment and prevention of arterial thrombosis. The irreversible P2Y12 blockers Clopidogrel and Ticlopidine were the first clinically approved antiplatelet drugs in this class. Genetic variation and drug-interaction issues complicate the use of these drugs and result in variable responses to treatment [39]. The second generation irreversible P2Y12 inhibitor Prasugrel has the advantage of a more rapid onset of action and results in a more consistent inhibition of platelet function as compared to Clopidogrel [40]. A major disadvantage of the irreversible P2Y12 inhibitors is that they require metabolic activation by the liver, which may result in unpredictable pharmacokinetics in patients with cirrhosis. The pharmacokinetics and pharmacodynamics of Clopidogrel are unaltered in patients with Child A or B cirrhosis [41], yet "significant liver impairment or cholestatic jaundice" is stated as contraindications in the package insert. No pharmacokinetic differences in patients with Child B cirrhosis were demonstrated for Prasugrel [42], and chronic liver disease is not a contraindication according to the package insert, although caution is advised. The

reversible P2Y12 inhibitor Ticagrelor does not require metabolic activation, but is cleared by the liver. Although it has been demonstrated that patients with Child A cirrhosis do not have impaired pharmacokinetic responses to Ticagrelor [43], severe chronic liver disease is a contraindication for this drug according to the package insert. Since most of the P2Y12 blockers state (severe) liver disease as a contraindication, the role of these drugs in patients with cirrhosis is unclear. However, since the contraindication appears primarily based on the perceived bleeding risk, studies on safety of Clopidogrel in these patients appear justified. Anecdotal evidence is suggestive of an acceptable safety profile [38]. The use of P2Y12 inhibitors for prevention of arterial events in cirrhosis may be limited to those patients without varices, since the rate of variceal bleeding in patients receiving antiplatelet agents following stent placement was substantial (12.5%).

Extended-release dipyridamole may be used for specific arterial indications. It is eliminated primarily by biliary excretion and undergoes enterohepatic recirculation. Although dipyridamole has potential beneficial side effects such as reducing progression of disease (shown in animal models) [44] and improvement of portal circulation [45], it does worsen renal function in patients with ascites and increased plasma renin activity [46].

Heparins

Heparins may be considered for prevention or treatment of venous thrombosis, PVT, and as adjunct treatment in acute arterial thrombosis. Three classes of heparins are currently available; unfractionated heparin, LMWHs, and the synthetic pentasaccharide Fondaparinux. In the general population, the advantages of LMWH or pentasaccharide are mode of administration (s.c. *vs.* i.v.) and the fixed dose that does not require laboratory monitoring, except in patients with extreme obesity and patients with renal dysfunction. Unfractionated heparin is routinely monitored with the aPTT, whereas LMWH dosing can be monitored with anti-Xa assays in patients without severe liver dysfunction.

The mode of administration of these agents (i.v. for unfractionated heparin, and s.c. for LMWH and fondaparinux) as well as the concern for heparin-induced thrombocytopenia (HIT), however, may limit long-term use. Nevertheless, patients with cirrhosis have been treated with daily s.c. injections of LMWHs for up to a year with the aim to either treat or prevent portal vein thrombosis [8,13]. These prolonged daily s.c. injections are clearly inconvenient for the patient and may be associated with poor compliance. Furthermore, skin reactions, which are mainly type IV delayed hypersensitivity reactions, at the injection site may occur, which may require a switch to a different LMWH preparation or alternative anticoagulant therapy [47]. Although the incidence of delayed-type hypersensitivity reactions towards LMWH is estimated at 7.5% but may go up to 40% in specific populations (in particular in pregnant women), such problems have not been reported in the studies performed in patients with cirrhosis. Importantly, these adverse events are known to be under-reported in patients without liver disease, and future studies in patients with cirrhosis should thus carefully examine the incidence of skin reactions.

Although the published experience in patients with cirrhosis is limited, LMWHs appear to have an excellent safety profile in patients with cirrhosis and venous thrombosis or PVT [8–10,13,21,48]. Nevertheless, there are important caveats in using these agents in this patient population. First, LMWH accumulation is known to occur in patients with renal failure, and thus patients with cirrhosis and decreased renal function likely require dose-adjustments. Second, heparins possess anticoagulant activity by virtue of an enhancing effect of the endogenous anticoagulant antithrombin. Since antithrombin is synthesized in the liver, plasma levels are frequently decreased in patients with cirrhosis, which theoretically leads to an unpredictable anticoagulant effect. This is especially true in the context of the multiple other changes in the hemostatic system in patients with cirrhosis. Indeed, *in vitro* studies have demonstrated that LMWH has a more profound anticoagulant effect in plasma from patients with cirrhosis as compared to plasma from healthy controls [49]. In addition, it has been suggested in patients with cirrhosis that anti-Xa levels after a standard prophylactic or therapeutic dose of LMWH fall below the recommended ranges for optimal anticoagulant control [48]. However, the decreased anti-Xa levels in these patients appear to be a laboratory anomaly and not a true indication of anticoagulation effect. *In vitro* addition of LMWH to plasma from patients with cirrhosis has demonstrated that the anti-Xa level subsequently measured in these plasmas is substantially lower as compared to the levels that were actually added (recoveries as little as 32% have been reported), whereas the recovery in normal plasma is around 100% [49,50]. Thus, in patients with cirrhosis who generally have an acquired antithrombin deficiency, the anti-Xa assay underestimates the true LMWH mass. This laboratory anomaly will cause a falsely low level of anti-Xa activity and may lead to incorrect and possibly dangerous dose escalations. On the other hand, the anticoagulant potency of LMWH appears increased in patients with cirrhosis, which points to a requirement for dose-reductions. Clinicians need to be aware of these caveats, and clinical studies on the risk/benefit of different dosing strategies of these agents are required in order to formulate liver-specific guidelines. A more reliable monitoring test would assist in these studies. The thrombin generation test might hold promise as such a test, but a major problem is that the test is relatively complex and not available in the routine clinical laboratory. Alternatively, point of care tests such as thromboelastography may be useful for LMWH monitoring, but studies assessing usefulness of this technique and to establish target ranges have not been published in the cirrhosis population.

Whether similar monitoring problems also occur with unfractionated heparin or fondaparinux has not yet been assessed. An additional problem with monitoring of unfractionated heparin is that the aPTT, which is instrumental in dosing this agent, is already prolonged in many patients with cirrhosis, and therefore aPTT target ranges for these patients are unclear.

Vitamin K antagonists

VKAs are still the cornerstone of long-term anticoagulant treatment in the general medical population. The major issue with VKA use is the absolute requirement for regular monitoring of the anticoagulant intensity by the International Normalized Ratio (INR). INR target ranges for different indications have been established, and dose adjustments are made when a patient is out of range. It has been well established that an INR below the target range increases this risk of (re)thrombosis, whereas an INR above the target range increases bleeding risk.

VKAs result in decreased functional levels of the vitamin K-dependent procoagulant proteins factor VII, IX, X, and II. In

addition, VKAs reduce functional levels of the anticoagulant proteins C and S, but the net result of VKAs is a reduction of hemostatic potential.

The major concern with the use of VKAs in patients with cirrhosis is that the target INR for patients with cirrhosis and an already prolonged INR is unclear. It is now well established that while a prolonged INR due to VKAs indicates a decreased hemostatic potential, a prolonged INR due to cirrhosis is unrelated to hemostatic capacity [1,51]. Furthermore, it is difficult to interpret an INR that is elevated due to a combination of cirrhosis and VKAs since the impact of VKAs on coagulation is so different from the impact of the coagulation abnormalities of cirrhosis on the clotting system. Finally, it has been demonstrated by multiple independent groups that the between-laboratory variability of the INR in patients with cirrhosis is unacceptably high [52–54], which complicates VKA monitoring by the INR in patients with cirrhosis even further.

The use of VKAs in patients with cirrhosis is thus likely associated with an unfavorable risk/benefit ratio, in particular in patients with high INRs prior to VKA initiation, as an optimal anticoagulant intensity will be difficult to achieve. Indeed, the use of VKAs in patients with cirrhosis has been associated with an increased risk of bleeding complications [18,55]. There is a need for a more reliable monitoring test for intensity of VKA anticoagulation in the patient with cirrhosis. Thrombin generation tests or thromboelastography may have a better performance as compared to the INR, but studies examining this are still lacking. Another possible alternative towards monitoring of VKAs in patients with cirrhosis is measurements of activity levels of one of the vitamin K-dependent factors (for example FII), but the target FII level for optimal anticoagulant activity has not yet been established.

New-generation oral anticoagulants

Two novel oral anticoagulants have recently been approved for clinical use. Rivaroxaban is a direct factor Xa inhibitor, and Dabigatran is a direct factor IIa inhibitor [56]. Unlike VKAs, both agents inhibit a single coagulation protease, and unlike heparins, both agents are independent of antithrombin. Both agents do not require laboratory monitoring in the general population. Although this is considered as a major advantage of these drugs, it is at the same time also a disadvantage as it increases the risk for non-compliance, which is rapidly detected in patients using VKAs as a drop in the INR. Further advantages of these drugs are the mode of administration (oral) and lack of heparin-induced thrombocytopenia. These new drugs would potentially be applicable in both long- and short-term anticoagulant strategies including prevention or treatment of venous thrombosis, prevention or treatment of PVT and prevention of disease progression.

Potential advantages of these drugs over VKAs are the wider therapeutic window. Nevertheless, monitoring of the new drugs may be required in patients with liver disease. Laboratory methodologies for monitoring these new drugs are still in development, and validation in patients with cirrhosis will be required. A major advantage of the new drugs over heparins is the mode of administration. In particular the long-term anticoagulant regimens that are currently applied to patients with PVT may be improved substantially by switching to oral agents.

Rivaroxaban

There are little published clinical studies with Rivaroxaban in patients with cirrhosis, as they were excluded from clinical trials. Nevertheless, there is a warning to avoid Rivaroxaban in patients with Child B and C cirrhosis according to the package insert, which is related to a (perceived) bleeding risk. Furthermore, significant increases in Rivaroxaban exposure are observed in patients with Child B cirrhosis [57]. In addition, Rivaroxaban was associated with a higher risk for GI bleeding compared to warfarin in patients with adequate liver function [58]. Finally, Rivaroxaban is cleared primarily by the kidneys (66%) and liver (34%) [59]. Patients with cirrhosis with or without concomitant renal failure, and in particular patients with the hepatorenal syndrome may thus not be ideal candidates for Rivaroxaban, and dose adjustments may be required.

A major concern regarding the use of Rivaroxaban is the lack of established reversal agents. Given its half life of 5–13 hours, drug discontinuation is insufficient when an acute bleeding occurs. One study in healthy volunteers has demonstrated that a prothrombin complex concentrate reverses the anticoagulant effect of Rivaroxaban [60]. A second study, in which reversal agents were added *in vitro* to plasma from healthy volunteers receiving Rivaroxaban, showed (partial) reversal of the anticoagulant effect by both (activated) prothrombin concentrates and recombinant factor VIIa [61].

Dabigatran

There is also little clinical experience with Dabigatran in patients with cirrhosis, but contrary to Rivaroxaban, Dabigatran is not explicitly contraindicated for patients with cirrhosis. The pharmacokinetics of Dabigatran is not different between patients with Child B cirrhosis and healthy individuals [62]. Dabigatran is mainly (80%) eliminated via the kidneys, and in severe renal failure bioaccumulation occurs [63]. Patients with cirrhosis and renal failure may thus not be ideal candidates for Dabigatran, and dose adjustments may be required.

Similar to Rivaroxaban, the long half life of Dabigatran (12–14 hours) renders drug discontinuation alone insufficient in case of acute bleeding. Dabigatran may be neutralized soon after ingestion by gastric lavage or charcoal administration, and in severe cases acute hemodialysis may be considered [64]. A study in which reversal agents were added *in vitro* to plasma from healthy volunteers receiving Dabigatran showed (partial) reversal of the anticoagulant effect by both (activated) prothrombin concentrates and recombinant factor VIIa [61].

In patients without liver dysfunction, Dabigatran has been associated with an increased risk of lower gastrointestinal bleeding, which may be related to the poor bioavailability of the drug, which results in high concentration of the drug in feces [65]. Furthermore, over 10% of patients in phase III trials of Dabigatran complained of dyspepsia [66], which has been attributed both to high levels of the drug in the colon and to the high concentration of tartaric acid in the capsule. This side effect is especially worrisome since the co-administration of Pantoprazole decreases the effective therapeutic area under the curve for Dabigatran by 22% [67]. Whether these pharmacokinetic interactions are class effects and whether they are clinically pertinent have not been completely determined. These considerations may limit the applicability of Dabigatran in patients with moderate or severe cirrhosis.

Table 1. Antithrombotic drugs that are registered for clinical use and recommended for prevention or treatment of venous or arterial events in the most current guidelines. Their mechanism of action, potential indications in patients with liver disease, and advantages or disadvantages are shown.

Drug	Mechanism	(Potential) indications	Pros	Cons
Aspirin	Cyclooxygenase inhibitor	Treatment/prevention arterial thrombosis	Cost, experience and proven efficacy in general population, limited data suggests safety in cirrhosis	Aspirin resistance difficult to detect, GI bleeding risk
Clopidogrel	Reversible P2Y12 inhibitor	Secondary prevention arterial thrombosis	No change in pharmacokinetics in Child-Pugh A and B cirrhosis	Variable response to treatment due to genetics and drug-interaction, bleeding risk
Prasugrel	Reversible P2Y12 inhibitor	Secondary prevention arterial thrombosis	More consistent inhibition of platelet function compared to clopidogrel	Bleeding risk
Tricagrelor	Irreversible P2Y12 inhibitor	Secondary prevention arterial thrombosis	Does not require metabolic activation by the liver	Bleeding risk
Extended release-dipyridamole	Adenosine uptake inhibitor and phosphodiesterase inhibitor	Treatment/prevention ischemic stroke	Beneficial effects on portal circulation	Affects renal function in patients with ascites
Unfractionated heparin	Antithrombin-dependent inhibition of FXa and thrombin	Prevention DVT, prevention/ treatment acute coronary syndromes, cardiac surgery	Cost, fully reversible with protamine	Risk of HIT, dependent on antithrombin monitoring with aPTT difficult, not ideal for long-term treatment, mode of administration (i.v.)
Low molecular weight heparin	Antithrombin-dependent inhibition of FXa and (to a lesser extent) thrombin	Prevention/treatment DVT and PVT	Reduced risk for HIT, route of administration (s.c. *vs.* i.v. for UFH)	Antithrombin dependence, issues with anti Xa monitoring, only partial reversal by protamine, not ideal for long-term treatment, accumulation in renal failure
Fondaparinux	Antithrombin-dependent inhibition of FXa	Prevention/treatment DVT and PVT	Further reduction in risk of HIT compared to other heparins, synthetic drug	Antithrombin dependence, issues with anti Xa monitoring, no established reversal agent, not ideal for long-term treatment, accumulation in renal failure
Vitamin K antagonists	Reduce functional levels of vitamin K-dependent proteins	Prevention/treatment DVT and PVT	Cost, experience and proven efficacy in general population, mode of administration	Issues with monitoring in patients with already elevated INR, bleeding
Rivaroxaban	Direct factor Xa inhibitor	Prevention/treatment DVT and PVT	Lack of antithrombin dependence, mode of administration, wider therapeutic window than VKAs	Lack of experience, no established antidote, GI bleeding risk, accumulation in renal and liver disease
Dabigatran	Direct thrombin inhibitor	Prevention/treatment DVT and PVT	Lack of antithrombin dependence, mode of administration, wider therapeutic window than vitamin K antagonists	Lack of experience, no established antidote, GI bleeding risk, dyspepsia, interaction with pantoprazole, accumulation in renal failure

Conclusions

Anticoagulant therapy in the patient with cirrhosis is a major challenge. As the hemostatic system in cirrhosis is frequently altered substantially, compared to healthy individuals, it is likely that anticoagulant drug regimens applied in the general population will result in unpredictable effects in the patient with cirrhosis. Moreover, monitoring of anticoagulant therapy is difficult as the available monitoring strategies are developed for use in individuals with a competent hemostatic system prior to initiation of anticoagulant therapy. For these reasons, it will be difficult to achieve an optimal intensity of the anticoagulant treatment which will increase the risks of thrombosis, recurrent thrombosis, or bleeding.

For many of the available agents, little or no published experience in the patient with cirrhosis exists. Nevertheless, we believe it is relevant that the hepatology community is aware of the (theoretical) advantages and disadvantages of the available drugs, which we have described in this review and are summarized in Table 1. The awareness that patients with cirrhosis may be candidates for prophylactic or therapeutic anticoagulant intervention is increasing. Similarly, the proportion of patients requiring anticoagulant therapy is likely increasing (for example due to the increasing incidence of NASH). Clinical and laboratory studies on mechanisms, efficacy, and safety of the various antithrombotic strategies will be required in patients with cirrhosis. Such studies will assist in future management decisions as well in

design of clinical trials assessing efficacy and safety of various antithrombotic regimens. For some of the newer drugs, including Rivaroxaban and Dabigatran, the theoretical disadvantages such as drug accumulation with a resulting bleeding risk may prohibit clinical trials in patients with advanced disease. Nevertheless, a potentially important new indication for antithrombotic therapy in patients with mild to moderate cirrhosis is prevention of progression of disease, and in such patients the new oral anticoagulants may be applicable. In these patients with compensated disease, the advantages of the new drugs may outweigh the drawbacks.

Conflict of interest

PWK has received research grants from LeoPharma en Sanquin and served on advisory boards of LeoPharma, Boehringer Ingelheim, and Pfizer. The other authors report no conflicts of interest.

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