Management of coagulation abnormalities in liver disease

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Abstract

Liver disease is characterized by changes in all phases of hemostasis. These hemostatic alterations were long considered to predispose patients with liver disease towards a bleeding tendency, as they are associated with prolonged conventional coagulation tests. However, these patients may also suffer from thrombotic complications, and we now know that the hemostatic system in patients with liver disease is, in fact, in a rebalanced state. In this review we discuss the concept of rebalanced hemostasis and its implications for clinical management of patients with liver disease. For instance, there is no evidence that the use of prophylactic blood product transfusion prior to invasive procedures reduces bleeding risk. Clinicians should also be aware of the possibility of thrombosis occurring in patients with a liver disease, and regular thrombosis prophylaxis should not be withheld in these patients.
Introduction

Chronic and acute liver diseases alter the hemostatic system tremendously [1]. Historically, patients with liver diseases were considered to be at high risk for bleeding complications due to the negative impact of the diseased liver on platelet synthesis and function, reduced production of coagulation factors and hyperfibrinolysis. However, the liver is also involved in the synthesis of various antihemostatic and antifibrinolytic proteins and therefore the hemostatic system is perceived to be rebalanced, as shown by recent laboratory studies and clinical observations [2]. This rebalance in the hemostatic system is not reflected by conventional coagulation tests, such as the prothrombin time (PT) and the activated partial thromboplastin time (APTT) [3]. Hence, these tests cannot be used to assess bleeding or thrombotic risk in patients with liver disease. Clinically, the rebalanced hemostatic system is reflected by the large proportion of patients with liver disease who can undergo major surgery without any requirement for blood product transfusion [4]. In fact, prophylactic use of blood products may even contribute to bleeding rather than prevent it. However, correcting the laboratory coagulopathy by transfusion of blood products prior to invasive procedures is still common practice in many centers [5,6].

The occurrence of both clinical thrombotic events and bleeding complications in patients with liver disease suggests that the balance of the hemostatic system is more fragile in these patients than in healthy individuals [7]. In fact, treatment and prevention for thrombotic complications is often necessary [8,9]. However, due to the profound hemostatic alterations and insufficient clinical experience, antithrombotic therapy is highly complicated in patients with liver disease and the best choice of drugs is still unknown.

This review summarizes the changes in the hemostatic system in patients with liver diseases. In addition, we review the limitations of laboratory tests in the investigation of bleeding or thrombotic risk in these patients. Finally, we discuss difficulties in management of both bleeding and thrombotic complications in liver disease patients.

The hemostatic system in patients with liver disease

The hemostatic system comprises platelet aggregation, coagulation and fibrinolysis also termed primary, secondary and tertiary hemostasis. Liver disease is associated with changes in all these phases of hemostasis (Table 1). Historically, these changes were interpreted as predisposing for a bleeding tendency due to the abnormal laboratory coagulation tests and the observation that spontaneous bleeding occurs frequently in this group of patients. However, several authors have pointed out shortcomings of this classical interpretation of the coagulopathy of liver disease [10-13] and in recent years the concept of ‘rebalanced hemostasis’ [2] has become widely accepted. In this concept, we suggested a new but more fragile balance within and between the procoagulant, anticoagulant and fibrinolytic systems.

Changes in primary hemostasis

In primary hemostasis, the formation of a platelet plug is initiated by vessel wall damage with the exposure of platelet adhesion proteins such as collagen. Concurrent tissue factor exposure activates the plasmatic coagulation cascade. Then, activated platelets capacitate the rapid production of a fibrin mesh by exposing activated clotting factors on their surface and producing a ‘thrombin burst’ through a positive feedback mechanism [14].
A reduced platelet count is common in patients with acute or chronic liver disease. The etiology of thrombocytopenia in patients with liver diseases is multifactorial. An important cause includes pooling of platelets and sequestration in the spleen due to congestive splenomegaly, which is related to portal hypertension [15]. Some authors have also suggested a role of antiplatelet antibodies [16] and decreased production of platelets because of lower levels of hepatic thrombopoietin [17]. Furthermore, platelet consumption, because of cirrhosis-related hypercoagulability resulting in systemic or intrahepatic platelet activation, has also been assumed to be an etiopathologic factor of thrombocytopenia in patients with chronic liver disease [18].

Besides thrombocytopenia, multiple mechanisms predisposing to functional platelet defects have also been described [11]. On the other hand, high plasma levels of von Willebrand factor (VWF) might compensate for defects in platelet number and function in patients with cirrhosis [19]. Indeed, it has been shown that VWF levels are elevated in proportion to the severity of liver disease [20]. The elevated levels of VWF may be a consequence of endothelial activation commonly observed in patients with liver disease. Endothelial activation is considered an important consequence of portal hypertension, and in fact, it was shown that VWF levels are associated with clinically significant portal hypertension [21]. Other possible mechanisms of elevated levels of VWF in cirrhosis are induction of synthesis of VWF in the cirrhotic liver itself or reduced liver-mediated clearance. Although the concept of platelet hypofunction in cirrhosis has long been widely accepted, more recent work suggests that platelet function might not be abnormal when studied under physiological test conditions. One study showed that although in-vitro platelet adhesion to subendothelial structures under conditions of flow is substantially reduced, this was fully attributable to the reduced platelet count and reduced hematocrit in these patients [22]. Another study even provided evidence for enhanced platelet function [23].

**Changes in the coagulation cascade**

In secondary hemostasis, complex reactions of the pro- and antihemostatic proteins in the coagulation cascade lead to the formation of a fibrin clot (Figure 1). The liver produces all plasma proteins involved in the generation of a fibrin mesh (except factor VIII). As a result, levels of coagulation factors V, VII, IX, X, XI and prothrombin are commonly reduced in both acute and chronic liver disease [24]. In contrast, factor VIII levels are often elevated [25], possibly due to upregulated synthesis from extrahepatic sites, such as the lung, spleen and kidney [26]. Other possible causes for the high levels of FVIII may be the elevated levels of VWF, the carrier protein of FVIII or reduced FVIII clearance. Fibrinogen levels are frequently reduced (except for patients with biliary cirrhosis, in which fibrinogen levels may be elevated), especially in patients with acute liver failure or advanced cirrhosis. In addition, fibrinogen is often functionally aberrant as a result of excessive sialic acid content leading to impaired fibrin polymerization [27].

The decreased production of procoagulant factors is mostly counterbalanced by decreased production of anticoagulant proteins, such as protein C, protein S, protein Z, protein Z-dependent protease inhibitor, antithrombin (AT), heparin cofactor II and a2-macroglobulin, which are all produced by the liver [1]. Tissue factor pathway inhibitor (TFPI) is synthesized by endothelial cells, and as a result of continuous activation of the endothelium in patients with liver disease, these patients are assumed to have increased levels of TFPI. However, studies
have shown either increased or normal levels of TFPI in patients with acute or chronic liver diseases. It has recently been established that protein S acts as a cofactor for TFPI in the downregulation of thrombin generation and, as a result, acquired and congenital protein S deficiencies are associated with a concomitant TFPI deficiency [28]. It may thus be that the increased TFPI release in patients with liver disease is masked by the decrease in protein S. Indeed, we recently reported that, despite a substantial decrease in protein S levels in patients with cirrhosis, TFPI levels are comparable between patients and healthy individuals. However, despite normal TFPI plasma levels, the TFPI/protein S anticoagulant system is functionally impaired in patients with cirrhosis [29, Chapter 3 of this thesis].

Studies using the thrombin generation test have examined the net balance of secondary hemostasis. As shown in Table 1, these studies have either shown a normo- or hypercoagulable state. These contrasting data may be attributed to differences in methodology, but probably also to differences in the disease severity of included patients. In fact, it has been hypothesized that progression of liver disease is correlated with a more hypercoagulable state, possibly due to the progressive decrease of protein C [30] and/or increase of FVIII levels [24,31] with increasing disease severity.

**Figure 1.** Schematic representation of the coagulation cascade and fibrinolytic system resulting in the generation and subsequent breakdown of a fibrin clot.

In this figure, activator processes are indicated by the uninterrupted lines, whereas regulatory or inhibitory steps are indicated by interrupted lines. After vessel wall damage, binding of coagulation factor VII to the exposed transmembrane protein TF initiates a series of enzymatic reactions in which proenzymes are activated into active forms. This cascade results in the generation of thrombin (IIa), which then cleaves fibrinogen into fibrin. Thrombin generation is downregulated by TFPI and AT, which inactivate factor VIIa and Xa, and thrombin, respectively. Furthermore, activated protein C, activated when thrombin binds to its endothelial receptor TM, inactivates cofactors Va and VIIIa. The fibrinolytic system can break down the fibrin clot, which is initiated by release of plasminogen activators tPA or uPA from endothelial cells, macrophages or renal epithelial cells. The plasminogen activators activate plasminogen to form plasmin, an enzyme that degrades fibrin into fibrin degradation products. Plasmin generation is regulated by PAI-1, a direct inhibitor of tPA and uPA, and by Pi, which inactivates plasmin. Furthermore, activated FXIII and activated TAFI, both activated by thrombin generation in the coagulation cascade, render the fibrin clot more resistant to plasmin. AT: Antithrombin; PAI-1: Plasminogen activator inhibitor type 1; Pi: Plasmin inhibitor; TAFI: Thrombin activatable fibrinolysis inhibitor; TF: Tissue factor; TFPI: Tissue factor pathway inhibitor; TM: Thrombomodulin; Tpa: Tissue-type plasminogen activator.
**Changes in the fibrinolytic system**

The liver synthesizes all proteins involved in the breakdown of a fibrin clot (fibrinolysis, see Figure 1), except for tissue-type plasminogen activator (tPA) and plasminogen activator inhibitor 1 (PAI-1). Indeed, levels of plasminogen, plasmin inhibitor, thrombin activatable fibrinolysis inhibitor and factor XIII are frequently reduced in both acute and chronic liver disease [32,33]. On the other hand, plasma levels of tPA are elevated as a result of enhanced release by activated endothelium cells and/or due to a reduction in the clearance of tPA by the diseased liver. Furthermore, PAI-1 levels are substantially increased in acute liver failure [34], but modestly increased in chronic liver disease [35]. The net effect of these changes has often been described as hyperfibrinolytic, but its mechanistic role in bleeding is still debated [11]. Although contrasting results have been reported (Table 1), the balance of fibrinolysis is probably restored in patients with chronic liver disease by the parallel changes in the profibrinolytic and antifibrinolytic proteins [32]. However, in patients with acute liver failure the balance is probably shifted toward hypofibrinolysis due to the elevated levels of PAI-1 [34], and hyperfibrinolysis may occur during liver transplantation as a result of lack of clearance of tPA during the anhepatic phase.

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<th>Hemostatic phase</th>
<th>Prohemostatic drivers</th>
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*Table 1. Summary of studies on the changes in all phases of the hemostasis in patients with liver disease. ADAMTS 13: a disintegrin and metalloprotease with thrombospondin type 1 motif 13; PAI: plasminogen activator inhibitor; TAFI: thrombin-activatable fibrinolysis inhibitor; t-PA: tissue plasminogen activator; VWF: von Willebrand Factor.*
Rebalanced but fragile: bleeding & thrombosis risk

Thus, despite the profound hemostatic alterations, the hemostatic system appears to be rebalanced in patients with liver disease. However, this balance is far more precarious and potentially unstable compared with the hemostatic balance in healthy individuals, which explains the occurrence of both bleeding and thrombotic complications in these patients. In fact, there are a variety of disturbances that can predispose an individual liver disease patient to either bleeding or thrombosis. For instance, development of renal failure is common in advanced liver disease and this usually leads to a bleeding tendency as a result of acquired platelet dysfunction, abnormal platelet-vessel wall interaction and anemia [36]. Another important and often coexisting modulator of hemostasis is the appearance of bacterial infections. Endotoxins may inhibit platelet function by prostacyclin production and enhancement of nitric oxide and inhibit coagulation by stimulating generation of heparin-like substances [37]. Bacterial infection may thus increase the risk of initiation and failure to control bleeding. However, some investigators also suspect a potential direct effect of endotoxin in the activation of the clotting cascade [38], leading to disseminated intravascular coagulation. Indeed, during endotoxemia or sepsis, endotoxin induces tissue factor expression in macrophages or endothelial cells, possibly contributing to development of disseminated intravascular coagulation [39,40]. Prophylactic administration of antibiotic drugs to patients with chronic liver disease is known to reduce mortality and improve the hemostatic function [41], but the exact mechanism is unknown. It is therefore recommended to adequately diagnose and treat infections before invasive procedures.

Variceal bleeding is one of the most common bleeding events occurring in patients with advanced liver disease, occurring in 20–30% of patients with cirrhosis [42]. However, the occurrence of variceal bleeding in patients with cirrhosis is mostly unrelated to hemostasis and depends more on local vascular abnormalities and portal hypertension leading to increased vascular pressure [43]. Indeed, prevention and treatment of variceal bleeding is currently not aimed at improving the hemostasis by transfusion of blood products, as these products may cause increased portal vein pressure and thereby aggravate bleeding, but the use of nonselective β-adrenergic blockers and endoscopic band ligation is recommended [44].

Nowadays, there is an increasing recognition of the various thrombotic complications that may occur in patients with liver diseases. Indeed, portal vein thrombosis (PVT) is a common occurrence in patients with cirrhosis, occurring in up to 26% of cirrhotic patients with end-stage liver disease [45]. Furthermore, the occurrence of venous thrombosis is also not uncommon in patients with liver disease. In fact, some studies have even suggested a significantly higher relative risk of venous thrombosis in these patients [9]. The incidence of thrombosis in liver disease is possibly underreported because of nonspecific symptoms of deep vein thrombosis and pulmonary embolism and the lesser attention of clinicians to the possibility of thrombosis in these patients. One clinical survey reported that 40% of patients admitted to the hospital with decompensated liver disease suffered from bleeding events (about one-half nonvariceal) and 7% suffered from deep venous thrombosis [46]. Finally, patients with nonalcoholic fatty liver disease, an increasing cause of liver disease in western counties, are known to have a substantially increased prevalence of arterial thrombotic events [47].
Laboratory measurements in patients with liver disease

There is a frequent clinical need for predicting the risk of bleeding or thrombotic events during or after procedures. However, current clinical available tests are not accurate in predicting those risks in patients with liver diseases because they only evaluate narrow aspects of the hemostatic system. Table 2 summarizes the limitations of commonly available laboratory measurements in patients with liver disease.

The bleeding time, which assesses platelet function, is frequently prolonged in patients with liver disease. Furthermore, the classic platelet aggregation assays are also frequently disturbed in these patients. However, both tests correlate poorly with bleeding symptoms in patients with liver disease [11]. Blood platelet count has some clinical correlation with bleeding, but possibly only at low platelet levels (below 50 x 10^9/l) [48].

The PT is widely used as a general indicator of coagulation. Because coagulation tests, such as the PT and APTT, only measure procoagulant factors and are not sensitive to the reduction in anticoagulant factors, they cannot reliably predict the risk of bleeding in patients with profound hemostatic alterations such as in liver disease [11,13]. These coagulation tests thus cannot reflect the true hemostatic status of patients with liver diseases. Furthermore, the interlaboratory variability of the PT assay is substantial in these patients, making its clinical implication more difficult.

Recently, thrombin generation testing has been increasingly used to reassess the hemostatic capacity of patients with liver disease. This test measures the total amount of thrombin generated during in vitro coagulation, in contrast with the PT and APTT, in which the time to formation of a plasma clot is measured when only about 5% of the total thrombin has been generated. Especially in the presence of thrombomodulin, a transmembrane protein located on vascular endothelial cells acting as the main physiologic activator of protein C, the thrombin generation test is sensitive to all anticoagulant proteins in the plasma. Therefore, this test measures the true balance between the pro- and anticoagulant factors. In fact, thrombin generation testing in the presence of thrombomodulin has demonstrated normal or even superior thrombin generation in patients with chronic liver disease [3,31,49,50]. Furthermore, in patients with acute liver disease, the PT and APTT are substantially prolonged; however, this is not associated with lower levels of thrombin generation [51] or an increased risk of hemorrhage [52-54]. Some studies have also shown that thrombin generation testing is useful in identifying patients with an increased risk of thrombosis [55-57] or those with a bleeding tendency [58]. However, the thrombin generation test is not widely available, addition of thrombomodulin is not standardized yet and currently the test is too complicated for routine use in diagnostic laboratories. Therefore, studies are needed to further assess the clinical value of the thrombin generation assay in predicting hemostatic abnormalities in patients with liver disease and to standardize the test for routine use.
Another possible potent technique for measurement of hemostasis in liver disease is thromboelastography (TEG) [59,60]. By using whole blood, this test measures speed and strength of clot formation continuously and can thus theoretically analyze all components of the hemostatic system [61]. Currently there are two commercially available devices, TEG and rotational thrombelastometry, and both have been routinely used for guiding transfusion of platelet concentrates, factor repletion and fibrinolytic therapy during liver transplantation [60]. Although most studies imply that thromboelastography provides an accurate assessment of bleeding risk in patients with liver disease, to date no studies have directly tested this hypothesis. Therefore, studies to assess the clinical value of the TEG to guide hemostatic management in patients with liver disease are urgently needed.

**Prevention & treatment of bleeding complications**

As mentioned before, patients with liver disease are not as prone to hypocoagulation-associated bleeding as clinicians formerly thought, and routine coagulation tests cannot be reliably used to assess a bleeding tendency in these patients. Therefore, management of bleeding complications should be aimed at encountering clinical relevant problems instead of correcting abnormal routine laboratory values. This policy is evidenced by the experience of patients with cirrhosis.
in liver transplantation, in which currently many patients can undergo transplantation without or with minimal transfusion of blood products [4].

**Minimal transfusion of blood products prior to invasive procedures**

Currently it is in many centers no longer common practice to use blood transfusion products prior to or during liver transplantation except in the occurrence of active bleeding. Indeed, there are no studies showing a beneficial effect of administration of fresh frozen plasma (FFP) or platelet concentrates on prevention of bleeding, specifically for patients with cirrhosis. There are, however, published data on the lack of efficacy of FFP administration in the general population [62,63]. In addition, a clinical trial in which platelet count was increased prior to invasive procedures by a thrombopoietin receptor agonist (Eltrombopag) was prematurely terminated due to thrombotic complications [64], suggesting that correction of thrombocytopenia in patients with liver disease does more harm than good. This may be due to the fact that thrombocytopenia is balanced by the highly elevated levels of VWF in patients with liver disease and that elevated levels of VWF in the context of normalized platelet counts result in a prothrombogenic state.

Despite the lack of benefits, prophylactic use of blood products prior to smaller invasive procedures, such as biopsies, thoracentesis and smaller surgical procedures, is still common practice. Indeed, FFP is frequently used to correct a prolonged PT in patients with liver disease, while recent transfusion guidelines specifically state that it is highly unlikely that these patients benefit from FFP [65]. Furthermore, in one randomized controlled trial in cirrhotic patients undergoing dental extractions usage of intranasal desmopressin appeared as effective, more convenient, better tolerated and less expensive than transfusion of FFP in the prevention of bleeding [66]. This indicates that there is little clinical benefit from prophylactic FFP transfusion before low-risk invasive procedures in patients with liver disease. Moreover, the response to FFP administration is unpredictable in these patients and frequently does not lead to a full normalization of the PT or international normalized ratio (INR) [67]. Prophylactic administration of FFP may even lead to volume overload and exacerbation of portal hypertension, and thereby paradoxically increasing the risk of bleeding [11]. Other side effects of FFP may be the risk of infection and the risk of transfusion-related acute lung injury. Since the benefits of FFP are unclear and given the side effects that may occur, we strongly advise against routinely correcting a prolonged PT or INR with transfusion of FFP prior to procedures in patients with liver disease. Instead, only those patients with significant bleeding should be treated. However, exceptions may include very high-risk procedures in which bleeding is unlikely to be detected in time to intervene before irreversible damage occurs (e.g., intracranial pressure monitor placement in patients with acute liver failure). Under these circumstances, it seems reasonable to (partially) correct prolonged coagulation times with FFP in spite of limited clinical data to support this practice. Because highly elevated levels of VWF appear to balance thrombocytopenia in patients with liver disease, and given the potential side effects, prophylactic platelet transfusion should also not be administered routinely. However, it has been suggested that correcting a platelet count below 50,000 or 60,000/ml may be advisable for high-risk procedures [14]. For example, the Society of Interventional Radiology guidelines advises to correct a platelet count <50,000/ml [68]. However, there is little clinical evidence to suggest that the bleeding risk indeed increased with platelets counts below a certain threshold. A single observational study demonstrated an increased bleeding risk following invasive procedures in patients with a platelet count below 75,000/ml [69]. Additional studies
to investigate whether such a threshold for correction of thrombocytopenia exists, and whether administration of platelet concentrates prior to invasive procedures has a beneficial risk/benefit ratio at platelet counts below such a threshold are required.

In contrast to the discussed transfusion products, administration of low-volume prohemostatics, such as prothrombin complex concentrates, that contain both procoagulant and anticoagulant proteins, may be useful in the prevention of bleeding during liver transplantation. The safety and efficacy of this preoperative administration of prothrombin complex concentrate in patients undergoing liver transplantation is currently under investigation [70].

**Treatment strategies for bleeding complications**

In summary, the occurrence of hemorrhage in patients with liver disease is frequently unrelated to hemostasis and depends more on portal hypertension, endothelial dysfunction, bacterial infection or renal failure. These risk factors should therefore also be addressed when preventing (re)bleeding. Moreover, excessive transfusion of red blood cells or large volumes of plasma should be avoided due to the increase in portal vein pressure and resultant increased (re)bleeding risk [14]. Indeed, in a recent randomized controlled trial in patients with acute upper gastrointestinal bleeding (a frequent complication in chronic liver disease) survival was improved and rebleeding risk reduced by the use of a restrictive red blood cells transfusion policy [71].

Instead of administration of blood products, treatment of coagulation abnormalities in liver disease patients may be addressed by the following drugs: Desmopressin (DDAVP, 1-deamino-8-D-arginine vasopressin), antifibrinolytics such as aprotinin and tranexamic acid and recombinant tissue factor VIIa (rFVIIa). DDAVP has been shown to correct the bleeding time [72]; however, several studies have shown that administration to patients with an acute variceal bleeding, undergoing hepatectomy or liver transplantation, has no effect on blood loss [73,74]. Therefore, the hemostatic effect of DDAVP in patients with liver disease is questionable. During liver transplantation, the usage of antifibrinolytics seems justified as it resulted in substantial reduction of blood loss in randomized studies [75,76]. In addition, in a recent Cochrane review [77], it was confirmed that antifibrinolytics may potentially reduce blood loss and transfusion requirements. However, one of the most frequently used antifibrinolytic drug, aprotinin, has been retracted from the market due to reported side effects in cardiac surgery [78]. However, alternatives such as tranexamic acid and epsilon aminocaproic acid are still available and equally effective [76]. Currently, antifibrinolytics are assessed for their potential in the prevention of gastrointestinal bleeding in the HALT-IT trial [79]. Finally, the use of rFVIIa during liver transplantation resulted in reduced blood loss in one pilot study [80], which was, however, not confirmed by larger randomized trials [81,82] and also not shown during liver resection. An effect of rFVIIa on variceal bleeding has recently been reported, but its use was associated with an elevated risk of thrombosis [83]. Thus, the evidence of the efficacy of rFVIIa in reducing bleeding complications is limited, and there is considerable evidence of its thrombogenic potential. Therefore, recently published guidelines from the European Society of Anaesthesiology on the management of severe perioperative bleeding recommended against the prophylactic use of rFVIIa in patients with liver disease and suggested that it should be used only as a rescue therapy for uncontrollable bleeding [84].
Prevention & treatment of thrombotic complications

As mentioned before, thrombotic complications do occur frequently in patients with liver disease and these patients may even be in a hypercoagulable state. Therefore, we strongly advise not to withhold thrombosis prophylaxis in patients with liver disease, even in the presence of abnormal routine tests of hemostasis, when risk factors for thrombotic complications are present. Examples of such risk factors for thrombosis prophylaxis include hospitalization and immobilization, undergoing invasive procedures, and the presence of (hepatocellular) cancer [85]. However, for general antithrombotic prophylaxis, especially in patients both at risk for thrombosis and bleeding, careful clinical decision making on an individual basis is needed. Finally, as a result of limited clinical experience, the choice and dosage of anticoagulant drugs for the various indications is still unknown.

Different anticoagulant drugs & their pros & cons in patients with liver disease

Vitamin K antagonists have been used for decades for the long-term prevention and treatment of thromboembolic events, and they are the most prescribed anticoagulants in the general medical population worldwide. A major drawback of vitamin K antagonist therapy in patients with liver disease is the monitoring of the drug by the INR because INR levels are already abnormal in these patients. Therefore, target ranges of the INR for patients with liver disease are unclear and an optimal anticoagulant efficacy will be difficult to achieve. Indeed, studies investigating vitamin K antagonists in patients with chronic liver disease have shown an unacceptably high level of bleeding complications [86,87].

The use of low-molecular-weight heparin in selected patients with cirrhosis has shown to be both safe and effective in the prevention and treatment of PVT [45,88]. Anticoagulant therapy may even be beneficial in these patients by preventing progression of cirrhosis [45]. In addition, the prevention of venous thrombosis with heparins appears safe and effective [89]. However, also heparins have drawbacks, especially long-term use of these drugs may be limited by the mode of administration as well as the concern for heparin-induced thrombocytopenia. Furthermore, we [90, Chapter 8 of this thesis] and Senzolo et al. [91] have recently shown that heparin and low-molecular-weight heparin have a more profound anticoagulant effect in plasma from patients with cirrhosis compared with healthy individuals. In addition, monitoring of heparins is complicated because the anti-Xa assay underestimates drug levels of LMWH in patients with cirrhosis [92,93]. This is most probably related to the reduced AT levels in patients with liver disease. Indeed, we have recently shown that the anti-Xa assay not only underestimates the LMWH mass, but the test also underestimates the masses of other AT-dependent anticoagulant drugs in plasma from patients with cirrhosis [94, Chapter 9 of this thesis]. However, when excess AT is added to the anti-Xa assay, the assay can be used in the monitoring of heparins in patients with cirrhosis [94], but this modification of the test is not readily available in many routine diagnostic laboratories.

New-generation antithrombotic drugs

Newer anticoagulant drugs, such as the direct factor Xa inhibitor rivaroxaban and the thrombin inhibitor dabigatran, have several theoretical advantages over the currently used anticoagulant drugs. The advantages include an oral mode of administration, rapid onset of action, fewer drug to drug interactions, lack of need for monitoring and no need for titration or dose adjustments [95]. However, the major advantage of no need for laboratory monitoring is at the same time also a disadvantage as it may increase the risk for noncompliance. Previously,
one of the major concerns for these drugs was the absence of an established reversal agent. However, this may be addressed in the future, as specific reversal agents for direct Xa and IIa inhibitors are in clinical development.

Both drugs may be applicable in the prevention and treatment of thrombotic complications in patients with liver disease. They may be advantageous especially in long-term anticoagulant strategies given the oral mode of administration. However, clinical data on the use of these drugs in patients with chronic liver disease are still lacking, as these patients have been excluded from clinical trials. According to the package insert, rivaroxaban is even contraindicated in patients with Child B and Child C cirrhosis due to a perceived bleeding risk. Since these new drugs are cleared by the liver and kidneys, the pharmacokinetics may potentially be altered in patients with liver disease. Nevertheless, in a recent case report, 6 months of therapy with rivaroxaban resulted in complete resolution of acute PVT in a patient with Child A cirrhosis, without any adverse effect [96]. Furthermore, in another study, five patients with cirrhosis and PVT safely received oral factor Xa inhibitor anticoagulants (rivaroxaban or apixaban) and in two patients repermeation of the portal vein occurred after 6 months of therapy [97]. We recently studied the potency of old and new anticoagulant drugs in plasma from patients with cirrhosis [90, Chapter 8 of this thesis] and observed a substantially increased anticoagulant response to dabigatran. In contrast, rivaroxaban resulted in a reduced response in plasma from patients with cirrhosis. Thus, the new oral anticoagulants may work differently in liver disease patients compared with patients with intact liver function, which is a potential caveat. Drug-specific dose adjustments, taking both the pharmacokinetics and the altered anticoagulant potency of the drug into account, may be required for patients with liver disease. Laboratory tests meeting these specific needs need to be developed.

Thus, antithrombotic treatment is frequently required in patients with liver disease and thrombosis prophylaxis should not be withheld from these patients. Clinical studies on efficacy and safety of the available anticoagulant drugs in patients with liver disease are urgently needed in order to better recommend the appropriate choice and dosage of anticoagulant drug for the prevention and treatment of the various thrombotic complications.

**Conclusion**

The concept of a rebalanced but more precarious hemostatic system in patients with liver disease, with the risk of both bleeding and thrombotic complications, is increasingly accepted. Routine laboratory tests, such as the platelet count, PT and APTT, are poor in predicting the bleeding risk in these patients, and more sophisticated tests of hemostasis, such as thrombin generation testing, are not available for routine use in diagnostic laboratories yet. Therefore, it is currently impossible for clinicians to identify individual patients with an increased risk for bleeding, except when risk factors, such as portal hypertension, endothelial dysfunction, bacterial infection or renal failure, are present. Future research should focus on developing a method that can reliably predict the bleeding risk of an individual liver disease patient.

In this paper, we have summarized the available evidence that the use of prophylactic transfusion products prior to invasive procedures, to correct prolonged routine coagulation tests, does not reduce bleeding risk. Instead, the use of blood products may paradoxically cause bleeding as a result of volume overload and has several other severe side effects.
These new insights should be established in common practice and only those patients with an active bleed should be treated. Furthermore, clinicians should be aware of the risk factors for hemorrhage and these should also be addressed.

It has also been highlighted that regular thrombosis prophylaxis should not be withheld in patients with liver disease, especially in the presence of risk factors, such as hospitalization and immobilization, undergoing invasive procedures, and the presence of (hepatocellular) cancer. However, we also acknowledge that future clinical research focusing on the efficacy and safety of anticoagulant therapies in these patients is necessary as specific guidelines for dosing and monitoring of these drugs for the prevention or treatment of thrombosis are lacking.

**Expert commentary**

Medical research on the hemostasis in liver disease has recently begun to expand, and laboratory testing and clinical observations have shifted the assumption of a hypocoagulation-based bleeding tendency in patients with liver disease toward the concept of a rebalanced hemostasis in these patients. However, these patients may suffer from both clinical relevant bleeding and thrombotic complications. Current laboratory tests fail to accurately predict bleeding and thrombosis risk in patients with liver diseases, and we therefore discourage using these tests in the prevention of procedural-related bleeding. Thrombin generation assays may be promising in assessing hemostatic imbalance in patients with liver diseases, as it is a good marker of global hemostasis. However, future studies are needed to further asses the clinical value of the test in predicting hemostatic abnormalities and to standardize it for routine use.

Current knowledge on the occurrence of bleeding complications in patients with liver disease has shown that its etiopathophysiology is frequently unrelated to a coagulopathy and depends more on risk factors, such as portal hypertension, renal failure or infections. This suggests that prophylactic transfusion of blood products prior to invasive procedures is not helpful in the prevention of bleeding, and indeed research has shown no benefits of these products. Its use may even contribute to bleeding rather than prevent it. We therefore strongly advise against prophylactic transfusion of blood products prior to invasive procedures in patients with liver disease. Instead, only those patients with significant bleeding should be treated, and the risk factors for bleeding should be addressed in the prevention of (re)bleeding.

Finally, since clinical observations have provided evidence for the occurrence of thrombotic complications in patients with liver diseases, we believe that these patients should not be withheld from thrombosis prophylaxis.

**Five-year view**

The occurrence of thrombotic complications and the necessity of antithrombotic therapy in patients with liver diseases is increasingly recognized. In the future, a further increase in the use of anticoagulant therapy in these patients may be expected due to the increased incidence of thrombotic complications over time related to increasing rates of fatty liver disease and generally longer survival times of patients with chronic liver disease.
Moreover, although our knowledge on bleeding in patients with cirrhosis has tremendously expanded, there still are patients with severe hemostasis-related bleeding, either spontaneously or procedure-related. First of all, it would be useful if we could predict which patients are at risk for thrombosis or bleeding. Currently, two tests may be promising in the prediction of bleeding or thrombosis risk in these patients, thrombin generation assays and TEG, as they both measure global hemostasis. However, future research is necessary to further assess the clinical value of these tests in predicting thrombosis and bleeding risk and their use in routine laboratories.

Furthermore, as the incidence of thrombotic complications may increase in patients with liver disease, both thrombosis prophylaxis and treatment should be used more frequently in these patients. Currently, specific guidelines on the choice and dose of anticoagulant drugs in patients with liver disease are lacking, and the available drugs have various advantages and disadvantages. Therefore, future clinical studies focusing on the efficacy and safety of anticoagulant therapies in these patients are urgently needed.

By far the most exciting advance in the field is the accumulating data showing that antithrombotic treatment may slow down progression of liver disease. If confirmed, this finding may cause a revolution in the management of patients with cirrhosis. If antithrombotic treatment truly prevents progression of disease and substantially delays decompensation, the need for liver transplant, or death, this will profoundly impact the clinical management of patients with (early) cirrhosis. However, future clinical studies on the benefits and safety of such treatment strategies in different patient groups are required to further apply this in clinical practice.

Finally, in the field of bleeding management in patients with liver disease prophylactic use of transfusion products prior to invasive procedures is not recommended because there is no evidence that this will reduce the bleeding risk. However, in the future it may be useful to investigate whether administration of low-volume prohemostatics can prevent bleeding during invasive procedures.
References


87. Levi M, Hovingh GK, Cannegieter SC, et al. Bleeding in patients receiving vitamin K antagonists who would have been excluded from trials on which the indication for anticoagulation was based. Blood 2008;111(9):4471-6.


