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REVIEW ARTICLE

Hypercoagulability in cirrhosis: causes and consequences[1]

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Summary. Decreased levels of most coagulation factors and thrombocytopenia are the main haemostatic abnormalities of cirrhosis. As a consequence, this condition was, until recently, considered as the prototype acquired coagulopathy responsible for bleeding. However, recent evidence suggests that it should, rather, be regarded as a condition associated with normal or even increased thrombin generation. The bleeding events that occur in these patients should, therefore, be explained by the superimposed conditions that frequently occur in this setting. Due to elevated levels of factor VIII (procoagulant driver) in combination with decreased protein C (anticoagulant driver), which are typically found in patients with cirrhosis, a procoagulant imbalance, defined as a partial resistance to the *in vitro* anticoagulant action of thrombomodulin, can be demonstrated. Whether this *in vitro* hypercoagulability is truly representative of what occurs *in vivo* remains to be established. However, the hypothesis that it may have clinical consequences is attractive and deserves attention. The possible consequences that we discuss herein include whether (i) cirrhosis is a condition associated with increased risk of venous thromboembolism or portal vein thrombosis; (ii) the hypercoagulability associated with cirrhosis has any other role outside coagulation (i.e. progression of liver fibrosis); and (iii) anticoagulation should be used in cirrhosis. Although apparently provocative, considering anticoagulation as a therapeutic option in patients with cirrhosis is now supported by a rationale of increasing strength. There may be subgroups of patients who benefit from anticoagulation to treat or prevent thrombosis and to slow hepatic fibrosis. Clinical studies are warranted to explore these therapeutic options.

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Introduction

Decreased levels of most procoagulant factors [1] and thrombocytopenia [2] are the main haemostatic abnormalities associated with chronic liver disease (CLD). As a consequence, this condition was, until recently, considered as a prototype acquired coagulopathy. Patients were (and are still) subjected to laboratory screening with the prothrombin and activated partial thromboplastin times (PT and APTT), and those with abnormal values were (are) treated with plasma or procoagulant agents to correct the abnormalities and to prevent haemorrhage during invasive procedures or to stop bleeding from the gastrointestinal tract. Little attention had been paid to the fact that, similar to procoagulant factors, their anticoagulant counterparts (namely protein C [PC] and antithrombin) are also reduced to the same extent in this setting. Therefore, the possibility that a rebalance of coagulation could take place in CLD has been ignored for many years.

Recently, evidence was provided that plasma from patients with cirrhosis could generate similar, or even greater, amounts of thrombin than plasmas from healthy subjects, provided thrombin generation is measured in the presence of thrombomodulin [3–6]. This has been interpreted as evidence that, under these experimental conditions (in which PC is fully activated), coagulation is rebalanced due to the concomitant reduction of both pro- and anti-coagulants that occurs in cirrhosis. Due to their design, the traditional coagulation tests such as the PT and APTT are not suitable to assess such coagulation balance. They are, in fact, based on the rate of conversion of fibrinogen-to-fibrin that starts after as little as 5% of the whole thrombin is generated, thus leaving the remaining 95% undetected. Furthermore, these tests are performed in the absence of thrombomodulin [7]. Therefore, they account for the reduced levels of the pro-coagulants, but are not sensitive to the parallel reduction of anticoagulants that occurs in cirrhosis and other acquired coagulopathies such as those in neonates [7].

Two logical consequences arise from this; first, conventional coagulation tests are of little help in assessing the haemorrhagic risk in patients with cirrhosis because they do not truly represent the balance of coagulation. These tests are indeed poor predictors of bleeding in these patients [7]. Second, the value of infusion of plasma or other procoagulant agents, which is still common practice to stop or prevent bleeding in this setting, is questionable. This is in line with the evidence stemming from recent randomised trials showing that recombinant activated factor VII fails to stop bleeding in patients with variceal haemorrhage [8,9] or during hepatectomy [10,11].

The reasons why patients with cirrhosis bleed may lie elsewhere. The most important candidates are portal hypertension, endothelial dysfunction, bacterial infections and the hepato-renal syndrome that are common in cirrhosis [12]. The role of thrombocytopenia that might explain, at least in part, the bleeding tendency observed in cirrhosis, has been recently attenuated based on the evidence that the *in vitro* adhesion of platelets from patients with cirrhosis under flow conditions is normal, owing to the increase of von Willebrand factor [13]. Finally, the role of hyperfibrinolysis, often advocated in cirrhosis to explain the haemorrhagic risk, is still unclear [14,15], owing to the lack of global tests truly reflecting the balance of fibrinolysis stemming from the action of the pro- and anti-fibrinolytic factors, that are both reduced in cirrhosis.

It might, therefore, be that in patients with cirrhosis the haemostatic balance is restored, but unlike to that of healthy individuals, is unstable owing to the partial reduction of the pro- and anti-coagulants and thrombocytopenia. Indeed, the occurrence of haemorrhage or thrombosis is not uncommon in these setting, depending on the prevailing circumstantial risk factors.

Recently, it was shown that an imbalance of pro- vs. anti-coagulants could be detected in plasma from patients with cirrhosis [16]. Whether this *in vitro* hypercoagulability is truly representative of what occurs *in vivo* remains to be established. However, the hypothesis that it may have clinical consequences is attractive and deserves attention. Among the possible consequences we discuss herein whether (i) CLD is a condition at increased risk of venous thromboembolism (VTE); (ii) the hypercoagulability associated with CLD has any other role outside coagulation; and (iii) anticoagulation should be used in CLD.

Causes of hypercoagulability

The endothelial receptor thrombomodulin accelerates the thrombin-mediated conversion of PC into its active form (activated-PC) [17], which is responsible for inhibiting thrombin generation. The addition of thrombomodulin is able to efficiently quench thrombin generation in normal plasma, but not in plasma from patients with cirrhosis. As shown in Fig. 1, the thrombin-quenching activity of activated-PC, measured as the ratio of values of thrombin activity generated in the presence and absence of thrombomodulin (this ratio being a biomarker of the *in vitro* hypercoagulability) is 0.44 in plasmas from healthy individuals and 0.70 in plasmas from patients with cirrhosis [3], indicating that the latter are partially resistant to the anticoagulant action mediated by thrombomodulin. Similar results were obtained when thrombomodulin was substituted with Protac [6,18], a non-physiologic activator of PC. The degree of resistance to thrombomodulin or Protac increases with the severity of liver impairment as classified with the Child-Pugh score [16,18], is directly correlated with the levels of factor VIII (FVIII) and inversely correlated with the levels of PC [16,18]. Furthermore, the degree of resistance is directly correlated with the FVIII:PC ratio [16,18]. FVIII in cirrhosis increases with the severity of the disease, reaching median values as high as 200% in the Child-C patients (the most severe) [16,18]. In contrast, PC decreases with the severity of the disease, reaching median values close to 40% in Child-C patients [16,18]. Interestingly, FVIII is a target protein for activated-PC and is one of the most important components of thrombin generation [19], and PC is one of the most important inhibitors of thrombin generation [17]. Hence, the ratio between the two moieties could be taken as an index of procoagulant imbalance. Patients with cirrhosis had a FVIII:PC ratio that increases with the severity of cirrhosis, reaching median values of 5.0 in Child-C patients [16,18]. The above observations point at the concept that cirrhosis possesses a procoagulant imbalance due to reduced PC in combination with increased FVIII. The possible consequences of this imbalance are reviewed below.

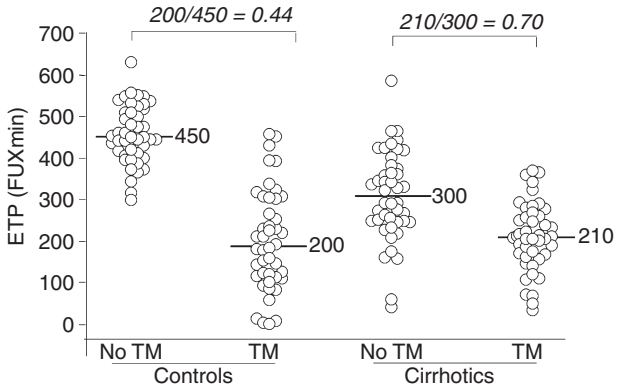

Fig. 1. Thrombin generation, measured as endogenous thrombin potential (ETP) with or without thrombomodulin (TM) in patients with cirrhosis and controls. Numbers close to the horizontal bars represent median values and numbers on the top represent ratios of ETP values measured with-to-without TM.

Consequences of hypercoagulability

Risk of VTE in patients with liver disease

VTE (i.e. deep vein thrombosis or pulmonary embolism) is a common cause of mortality and morbidity. In the general population, the incidence rate (IR) is 1–2 per 1000 person-years. Among selected groups such as the elderly, cancer patients, or those with comorbidities, the IR can be as high as one per 100 person-years [20–23]. The main complications of

VTE are the post-thrombotic syndrome, chronic pulmonary hypertension, and sudden death. Approaches for preventing VTE include reduction of risk factors and anticoagulant treatment. VTE is a multifactorial disease with several risk factors; the most well established are fractures, surgery, cancer, oestrogen intake, thrombophilia and pregnancy [24,25]. Assessment of other patient groups at risk is crucial to improve the prevention of VTE.

As mentioned previously, CLD can cause an imbalance in the coagulation system and a number of single-centre and population-based studies have shown that the liver disease-induced coagulopathy may be associated with thrombosis. Therefore, the paradigm that patients with cirrhosis are protected against VTE is changing.

Incidence and prevalence of VTE among patients with CLD have been estimated in several studies (Table 1). Five studies report an incidence of VTE varying from 0.5% to 6.3% [26–30]. Four additional studies found a prevalence ranging from 0.6% to 2.7% [31–34]. The varying incidence and prevalence in the different studies are partly explained by differences in study design, data sources, location, and criteria for inclusion/exclusion of patients.

Few studies have estimated the risk of VTE in patients with liver disease (Table 2). The first to address this issue were three case–control studies [24,25,27]; only one of these was designed to examine the risk of VTE associated with liver disease, the other two were designed to determine general risk factors for VTE. The first study was conducted in the US and was based on 625 patients with VTE and an equal number of hospital controls, and showed that severe liver disease was associated with a substantially reduced relative risk (RR) for VTE of 0.10 (95% CI:0.00–0.70)[24]. In contrast, a study performed in the UK, including 6500 patients with VTE and 10 000 controls, found a non-significant increase in RR for VTE of 1.65 (95% CI:0.97–2.82) in patients with CLD [25]. The third study was designed to estimate the risk of VTE in

Table 1 Incidence and prevalence of venous thromboembolism (VTE) (deep vein thrombosis and/or pulmonary embolism) in patients with chronic liver disease (CLD)

Author	Study design	Patients/Admissions	Incidence of VTE	Prevalence of VTE	VTE diagnoses included (exclusion criteria)
Northup *et al.* [26]	Case–control 1993–2001	Admissions for cirrhosis $n = 21\,000$	0.5% (113)		DVT and PE (excluding patients with a history of VTE, patients on anticoagulation therapy and patients undergoing liver transplantation)
Gulley *et al.* [27]	Case–control 1995–2005	Cirrhosis $n = 963$ Hospital controls $n = 12\,405$	1.87% (18)		DVT and PE (excluding patients with a history of VTE)
Dabbagh *et al.* [29]	Retrospective cohort 2000–2007	CLD or cirrhosis $n = 190$	6.3% (12)		DVT and PE (excluding patients with known active VTE, patients on anticoagulation therapy and patients receiving palliative care)
Lizarraga *et al.* [30]	Case–control 2004–2008	CLD $n = 14\,790$	0.73% (108)		DVT and PE
Garcia-Fuster *et al.* [28]	Retrospective cohort 1992–2007	Cirrhosis $n = 2074$	0.8% (17)		DVT and PE
Wu and Nguyen [31]	Cross-sectional 1998–2006	Compensated cirrhosis $n = 408\,253$ Decompensated cirrhosis $n = 241\,626$ Hospital controls $n = 575\,057$		0.81% (3307) 0.82% (1981) 0.76% (4370)	DVT and PE Phlebitis, iatrogen PE and infarction (excluding primary diagnosis of VTE)
Saleh *et al.* [32]	Retrospective cohort 1979–2006	Admissions for CLD (alcoholic) $n = 4\,927\,000$ Admissions for CLD (non-alcoholic) $n = 4\,656\,000$		0.6% (30 000) 0.9% (42 000)	DVT and PE
Aldawood *et al.* [33]	Retrospective cohort 2009	Cirrhosis $n = 226$		2.7% (6)	DVT and PE (excluding patients on anticoagulation therapy)
Ali *et al.* [34]	Cross-sectional 2005	Admissions for cirrhosis $n = 449\,798$		1.8% (8321)	DVT, PE and other venous thromboses (excluding patients with a history of VTE)

Table 2 Risk of venous thromboembolism (VTE) in patients with liver disease

Author	Study design	Patients	Adjusted risks (95%CI)	VTE diagnoses included
Heit *et al.* [24]	Population based nested case–control 1976–1990	Cases of VTE $n = 625$ (5 with serious liver disease) Hospital controls $n = 625$	OR 0.10 (0.00–0.70)	DVT and PE
Huerta *et al.* [25]	Nested case–control 1994–2000	Cases of VTE $n = 6\,550$ (39 with chronic liver disease) Controls 10 000	OR 1.65 (0.97–2.82)	DVT and PE (in addition the patients should receive anticoagulant therapy)
Gulley *et al.* [27]	Case–control 1995–2005	Cirrhosis $n = 963$ Hospital controls $n = 12\,405$	OR 0.87 (0.28–2.63)	DVT and PE
Sogaard *et al.* [35]	Case–control 1980–2005	Cases of VTE $n = 99\,444$ (544 with cirrhosis and 1109 with non-cirrhotic liver disease) Population controls $n = 496\,872$	Cirrhosis RR 1.74 (1.54–1.95)* RR 2.06 (1.70–2.38)† Non-cirrhotic liver disease RR 1.87 (1.73–2.03)* RR 2.10 (1.91–2.31)†	DVT and PE
Wu and Nguyen [31]	Cross-sectional 1998–2006	Cases with: compensated cirrhosis $n = 408\,253$ Decompensated cirrhosis $n = 241\,626$ Hospital controls $n = 575\,057$	Age < 45 year. OR 1.23 (1.04–1.46) OR 1.39 (1.15–1.69)	DVT and PE Phlebitis, iatrogen PE and infarction

*Overall Risk of VTE. †Risk of unprovoked VTE (excl. patients with a discharge diagnosis of fracture/major trauma, surgery or pregnancy within 90 days of VTE or a diagnosis of cancer either before or within 90 days after VTE).

almost 1000 patients with cirrhosis compared to other hospitalised patients. According to the unadjusted analysis, the risk of VTE was almost doubled in cirrhosis. However, the association between cirrhosis and VTE was lost in the adjusted analysis [27]. The conflicting results in these three studies, made it difficult to draw conclusions regarding the association between liver disease and VTE. Therefore, a large case–control study was conducted in Denmark to estimate the RR of VTE in patients with cirrhosis and non-cirrhotic liver disease. The study that included nearly 100 000 patients with VTE and 500 000 population controls provided strong evidence of an approximately doubled RR of VTE among patients with cirrhosis and non-cirrhotic liver disease [35]. For patients with cirrhosis, the RR of overall VTE and unprovoked VTE were 1.74 and 2.06. Unprovoked VTE was defined as VTE occurring in patients without a discharge diagnosis of fracture/trauma, surgery and pregnancy within 90 days before hospitalisation for VTE, and without a diagnosis of cancer before or within 90 days after VTE. Patients with non-cirrhotic liver diseases had a RR of VTE similar to that of patients with cirrhosis. In patients younger than 55 years, the RR of VTE was 3.58 and 3.32 for patients with cirrhosis and non-cirrhotic liver disease. In patients aged 55–74 years, the risk of VTE was also significantly higher; the RR was 1.86 for those with cirrhosis and 1.45 for those with non-cirrhotic liver disease. For patients > 74 years, a tendency towards higher RRs was observed, but the confidence interval included unity (K. K. Sogaard, unpublished data). Adjustments for several risk factors, including cirrhosis associated predisposing conditions, were performed. Although data on immobilisation were unavailable, the adjustments for recent fracture, surgery, cancer and other diseases included in the Charlson Index (an index including 19 comorbidities) are likely to have minimised the likelihood of unmeasured confounding effects. It was remarkable that risk estimates were nearly identical for cirrhosis and non-cirrhotic liver disease, since these patients expectedly have different degrees of metabolic disturbances, liver dysfunction and frequency of complications. However, recently non-alcoholic fatty liver disease has been identified as a risk factor for VTE [36], and this may explain the increased RR found in patients with non-cirrhotic liver disease.

Finally, in the most recent study addressing the topic, a large cross-sectional study from the US including almost 650 000 hospital admissions with cirrhosis and 575 000 admissions without liver disease found the prevalence odds ratio for having an in hospital VTE was 21% higher in patients with compensated cirrhosis and 39% higher in patients with decompensated cirrhosis, compared to hospitalised patients without liver disease. However, the higher VTE risk was restricted to patients younger than 45 years, whereas VTE prevalence was 10% lower in patients older than 45 years [31]. The slightly lower risk estimates in this study compared to those found by Sogaard *et al.* [35], may be a consequence of the choice of controls (population vs. hospitalised). Furthermore, the studies differed in terms of adjustment for confounders and cirrhosis related factors. Both studies adjusted for age, gender, calendar year and diseases included in the Charlson Index. In addition, Wu and Nguyen [31] adjusted for race, whereas Sogaard *et al.* [35] considered psychiatric diseases, fracture/major trauma, and surgical procedures as important cirrhosis related factors.

In conclusion, a growing body of evidence based on epidemiological studies indicates that patients with cirrhosis and other liver diseases are not necessarily auto-anticoagulated and hence not protected from VTE. Higher RRs of VTE have been found in patients with liver disease compared to population controls, but also compared to other hospitalised patients.

The role of hypercoagulability in hepatic fibrogenesis

The development of liver fibrosis following chronic injury, irrespective of aetiology, is considered a complex disease trait that may be influenced by the interaction of genetic factors and environment. Evidence suggests that one such factor is coagulation. Large thrombi occluding the hepatic vein are recognised as a cause of hepatic fibrosis in the Budd-Chiari syndrome [37]. Beyond this, the role of coagulation in fibrogenesis is supported by studies showing accelerated fibrosis progression in the presence of hypercoagulability. These include, chronic viral hepatitis and NAFLD where patients with advanced fibrosis are significantly more likely to have thrombophilia than those with milder disease (Table 3). Candidate gene association studies have shown carriage of the factor V Leiden (FVL) mutation to be associated with a 3.28-fold increased risk of rapid fibrosis progression in patients with hepatitis C [38]. This finding has since been independently validated in a second cohort [39] and additional reports have linked PC deficiency, increased FVIII expression and hyperhomocysteinaemia with more advanced fibrosis [40]. Animal studies in carbon tetrachloride-induced liver fibrosis and in the bleomycin inhalation-mouse model of pulmonary fibrosis have shown that C57BL/6 mice carrying the prothrombotic FVL mutation exhibit more severe fibrosis than wild-type littermates [41,42].

Pathogenic mechanisms Early investigators postulated that micro-infarcts resulting from thrombi in branches of the hepatic vein and portal vein near areas of inflammation caused ischaemia and cell death. It was suggested that subsequent parenchymal collapse, forming characteristic *parenchymal extinction lesions* [43,44], was eventually replaced by fibrous tissue producing cirrhosis [reviewed in 45].

The 'direct stellate cell activation' hypothesis linking hypercoagulability with hepatic fibrogenesis has a stronger evidence base, clear biological mechanisms and is supported by research carried out in several organ systems including lung and liver. Hepatic stellate cell activation is a process of cellular transdifferentiation triggered by liver injury through which the quiescent perisinusoidal hepatic stellate cell is converted into a wound-healing myofibroblast with potent pro-inflammatory and pro-fibrogenic activity [46,47]. Fibroblasts and stellate cells from both humans and rodents express members of the G-protein coupled protease activated receptor (PAR) family [48,49]. Thrombin signals via PAR-1 and PAR-3 (which have high affinity for thrombin activation) and PAR-4 [50]. In addition, coagulation factor Xa (FXa) can activate PAR-1 and PAR-2 [51–53]. Acting via PAR-1, thrombin is chemotactic for monocytes and mitogenic for smooth muscle cells, fibroblasts and hepatic stellate cells. Furthermore, in the lung, activation of PAR-1 has been shown to facilitate the $\alpha_v\beta_6$ integrin-dependent post-translational activation of latent transforming growth factor β, a key mediator of fibrogenesis [54].

In vitro studies using selective PAR-1 agonists and thrombin demonstrate that these produce rapid stellate cell activation, secretion of extracellular matrix proteins, tissue remodelling and fibrogenesis [48,49,55]. Several studies have established that hepatic PAR-1 expression is increased by liver injury, sensitising stellate cells to thrombin-mediated activation [48,49]. Tissue factor and PAR-1 expression are also increased in patients with cholestatic liver diseases, including primary biliary cirrhosis and sclerosing cholangitis and in a murine experimental model of cholestasis [56], suggesting that substrate (PAR-1) availability ceases to be a rate-limiting factor at sites of inflammation. Thus, hypercoagulability characterised by an increase of thrombin generation within the circulation, may contribute to fibrogenesis by enhancing direct activation of stellate cells. In this way, increased thrombin production due to failure of the thrombin/thrombomodulin negative feedback loop via activated-PC, as occurs in carriage of the FVL mutation in addition to increased FVIII, could amplify PAR-1 signalling. This model for the role of thrombin and FVL in the genesis of hepatic fibrosis is supported by studies that demonstrate fibrosis is ameliorated by administration of a PAR-1 antagonists [48] in both tissue factor and PAR-1 knockout mice [56]. Similarly, PAR-1 knockout mice are protected from bleomycin inhalation-induced pulmonary fibrosis [57]. The importance of PAR-1 is further supported by a gene-association study that showed rapid hepatic fibrosis associated with carriage of a C1426T mutation in the

Table 3 Studies showing an association between hypercoagulability and advanced liver fibrosis

Patient cohort	*n* (male%)	Factors	*P*-Value	References
HBV and HCV	90 (71)	Protein C deficiency	0.007	[74]
		Antithrombin deficiency	0.005	
		Plasminogen deficiency	0.03	
		Activated protein C resistance	0.075	
HCV	352 (56)	Factor V Leiden (APC Resistance)	0.004 (OR 3.28)	[38]
HCV	559	Factor V Leiden (APC Resistance)	0.003 (OR 4.0)	[39]
HCV	68 (63)	Protein C deficiency	0.004	[40]
		Elevated factor VIII level	0.002	
		Hyperhomocysteinaemia	0.023	
HCV	210 (0)	Factor V Leiden (APC resistance)	NS	[75]
HCV	287 (56)	PAR-1 polymorphism (C-1426T)	0.04	[58]
NAFLD/NASH	60 (52)	Increased fibrosis in patients with at least one pro-thrombotic risk factor	0.002	[76]

NS, not significant.

5′-regulatory region of the PAR-1 gene in two separate cohorts of HCV patients [58].

The role of FXa/PAR-2 signalling in hepatic fibrosis is less well characterised, however, there is now evidence for its role in several fibrotic diseases. PAR-2 is highly expressed during acute and chronic inflammation in lung tissue [59], pancreatic fibrosis [60] and renal interstitial fibrosis where PAR-2 and αSMA expression are both found [61]. *In vitro* studies have also shown that FXa triggers a pro-inflammatory and pro-fibrotic response in fibroblasts via PAR-2 activation including cellular proliferation, migration and myofibroblast differentiation characterised by αSMA production, MCP-1 and IL-6 secretion, and transforming growth factor β expression [51]. The relative contribution of PAR-1 vs. PAR-2 signalling remains unclear with some studies demonstrating that FXa signalling via PAR-1 remains the most important although this may vary in different tissues [62]. Recent studies indicate that platelet activation may further influence the complex balance of pro- and anti-fibrotic factors. Whilst platelet-derived growth factor (PDGF) is a potent stellate cell mitogen [63], platelet activation may also control hepatic stellate cell activity and promote fibrolysis through release of other mediators including hepatocyte growth factor [64]. Taken together, these data suggest that hypercoagulability can modulate various aspects of organ fibrogenesis, and that thrombin/FXa-mediated PAR-1/2 signalling are potent direct effectors of stellate cell activation and fibrosis.

Potential therapeutic implications A corollary of the association between hypercoagulability and increased fibrosis is that interference with coagulation through thrombin generation or downstream signalling may reduce fibrogenesis. Administration of a PAR-1 antagonist reduces hepatic fibrosis and SC activation in the rat bile-duct ligation model [48]. Carbon tetrachloride-induced hepatic fibrosis in C57BL/6 mice may be slowed by concomitant administration of vitamin K antagonists (VKA) [41]. Similar results have also been reported in this and other models of liver damage using low molecular weight heparin (LMWH) [65,66], the synthetic thrombin inhibitor SSR182289 [67] and dipyridamole [68]. Aerosolised heparin and urokinase are similarly effective in ameliorating bleomycin-induced pulmonary fibrosis [69]. A recent study has also demonstrated that increased pulmonary expression of FX contributes to the post-bleomycin inhalation fibrotic response through PAR-1 signalling and that this effect may be ameliorated using a direct-FXa inhibitor [62]. Similarly, a recent study showed that FXa inhibition with Rivaroxaban is an effective anti-fibrotic in the murine thiocetamide-induced liver fibrosis model [70].

Currently there are insufficient data to support the routine use of anticoagulation as an anti-fibrotic therapy outside clinical trials. However, it is becoming evident that modulating coagulation may be a relevant therapeutic target for development of novel anti-fibrotic agents (Table 4). One small study suggests efficacy of LMWH as an anti-fibrotic in patients with chronic HBV [71] and another study has reported reduced mortality with VKA treatment in patients with idiopathic pulmonary fibrosis [72]. Whilst comparative natural history data are limited, studies suggest that haemophilia patients mono-infected with hepatitis C virus exhibit a slow progression of liver disease and perhaps fibrosis [73]. A multi-centre trial (WAFT-C) examining the efficacy of VKA as an anti-fibrotic in the post-transplant chronic HCV population is underway.

In summary, hypercoagulability has been associated with rapid progression to cirrhosis both in animal models and in the clinic, most likely due to direct activation of stellate cells by thrombin and FXa via the PAR receptors. The corollary of an association between hypercoagulability and increased fibrosis is that interference with coagulation may reduce hepatic-fibrosis. This novel therapeutic area is the subject of clinical trials.

Anticoagulation in liver disease

The hypercoagulability associated with CLD might have a causative role for the development of hepatic or portal vein thrombosis that occur very frequently in this setting. This section provides an overview on (i) the association between hepatic or portal vein thrombosis and the severity of cirrhosis; (ii) the impact of pre-transplant portal vein thrombosis on transplantation outcome; (iii) the identification of prothrombotic risk factors for portal vein thrombosis; (iv) the effects of anticoagulation in patients with primary hepatic or portal vein thrombosis; and (v) the use of anticoagulation in patients with cirrhosis.

Table 4 Studies examining anticoagulation as anti-fibrotic therapy. VKA, vitamin K antagonists; LMWH, low molecular weight heparin

Organ/disease studied	Agent	References
Liver (mouse: carbon tetrachloride)	VKA	[41]
Liver (rat: carbon tetrachloride)	LMWH	[66]
Liver (rat: bile duct ligation)	LMWH	[65]
Liver (rat: carbon tetrachloride)	Thrombin inhibitor (SSR182289)	[67]
Liver (rabbit: cholesterol diet & diethylstilbestrol)	Dipyridamole	[68]
Liver (mouse: thiocetamide)	Factor Xa inhibitor (Rivaroxaban)	[70]
Lung (mouse: bleomycin inhalation)	Heparin/Urokinase	[69]
Lung (mouse: bleomycin inhalation)	Factor Xa inhibitor (ZK 807834)	[62]
Lung (mouse: bleomycin inhalation)	Dabigatran	[77]
Idiopathic pulmonary fibrosis (human trial)	VKA	[72]
Chronic viral hepatitis related liver fibrosis (human trial)	LMWH	[71]

Association of hepatic vein thrombosis or portal vein thrombosis with cirrhosis Evidence for hepatic vein thrombosis was found in 70% of livers explanted at a stage of advanced cirrhosis [44]. Areas with hepatic vein thrombosis were affected with parenchymal extinction, defined as a confluent hepatocyte loss combined with fibrous tissue replacement. Evidence for portal vein thrombosis was found in 36% of explanted livers [44], portal vein thrombosis being associated with focal atrophy of the hepatic parenchyma and areas of hyperplasia. In line with these findings, liver weight (standardised to body-weight) was lighter in patients with extrahepatic portal vein thrombosis than in patients without [78]. Furthermore, portal vein thrombosis was more commonly found at transplantation in patients with than in those without history of encephalopathy, ascites, spontaneous bacterial peritonitis or gastrointestinal bleeding [78,79]. The Model for End-stage Liver Disease (MELD) and Child-Pugh scores were higher in patients with than in those without portal vein thrombosis at evaluation for transplantation [80], at transplantation [81] or at surgical portosystemic shunting [82]. Furthermore, portal vein thrombosis was an independent predictor for failure to control bleeding [83]. The prevalence of portal vein thrombosis was lower than 1% in patients with compensated disease [84], but much higher (10%–25%) at the time of transplantation [85], portosystemic shunting [82] or endoscopic sclerotherapy [86], and intermediate (8%) in series of necropsy cases [87,88]. In patients listed for transplantation, occlusive portal vein thrombosis was an independent prognostic factor for mortality [89]. Advanced liver disease (by causing severe intrahepatic block, blood stasis and venous wall changes secondary to high portal pressure) might precipitate thrombosis in the portal venous system [87]. Alternatively, thrombosis in the portal venous system might impact on liver function by decreasing portal perfusion, a well established risk factor for liver atrophy [90,91]. Hence, a vicious circle may also be created whereby advanced liver disease causes venous thrombosis, which in turn aggravates liver disease.

Portal vein thrombosis negatively impacts the outcome after transplantation Depending on patient selection in terms of the degree of portal vein occlusion and extension in the portal venous system, mortality after transplantation is increased or unchanged as compared to patients without portal vein thrombosis, while the risk of recurrent thrombosis and the need for re-transplantation are generally increased. Recent data showed that portal-vein thrombosis increases mortality after transplantation by 30% [89,92].

Prothrombotic conditions as risk factors for portal-vein thrombosis Multivariate analyses showed that previous abdominal surgery, splenectomy, portosystemic-shunt surgery and endoscopic sclero-therapy (for oesophageal varices), but not age, are the main determinants of portal vein thrombosis [93,94]. These data point to a role for abdominal inflammation, injury to abdominal veins and turbulent or stagnant flow after surgery. Alternatively, however, splenectomy, surgical portosystemic-shunting, and endoscopic sclerotherapy could be mere indicators of a more severe portal hypertension rather than, or in addition to, being directly causative. The role of reduced levels of antithrombin, PC and protein S, and the presence of antibodies to cardiolipin that are common in liver disease cannot be easily interpreted [95,96]. An independent association between the occurrence of portal vein thrombosis and the presence of prothrombin gene [96] or MTHFR 677-TT polymorphisms [97] has been reported and appears to interact strongly with endoscopic sclerotherapy [86,94]. A slow baseline portal vein flow is an independent risk factor for portal vein thrombosis [95,97], together with MTHFR677-TT polymorphism, homocysteine and beta-blocker use [97].

Overall, these data consistently show that decreased portal-flow velocity is a major risk factor for the development of portal vein thrombosis and that certain genetic prothrombotic factors leading to heightened thrombin generation can increase the risk. The hypothesis that hypercoagulability due to high FVIII combined with low PC is an additional risk factor is attractive and warrants further investigation.

Anticoagulation in non-cirrhotic patients The routine implementation of anticoagulation for primary hepatic vein thrombosis likely contributed to the improvement in outcome seen over the last two decades [98]. Bleeding occurred in half of the patients and contributed to death in only 5% at a median follow-up of 43 months [99]. Anticoagulation appears to be safe and effective in preventing extension of acute portal vein thrombosis [100,101] but is less efficient for achieving complete recanalisation (40% of the patients) [100]. Anticoagulation appears to be effective in preventing recurrent thrombosis in patients with chronic portal vein thrombosis where it is not associated with increased incidence or severity of gastrointestinal bleeding [101]. In conclusion, available studies, despite being uncontrolled and usually retrospective, are consistent in indicating a favourable benefit: risk ratio for anticoagulation in non-cirrhotic patients with portal vein thrombosis.

Anticoagulation in cirrhotic patients Three series of portal vein thrombosis patients treated with anticoagulants have been reported with sufficient details [85,102,103]. Patients with cavernoma or hepatocellular carcinoma were excluded leaving a total of 56 patients. Portal vein thrombosis was partially occlusive in 86% of the patients and involved the main portal veins in 78%. The vast majority of patients had past bleeding or high-risk varices, and all were treated with endoscopic therapy with or without beta-blockers prior to anticoagulation. Complete and partial recanalisation was documented in 41% and 35% of patients, respectively. Bleeding was reported in only 5% of the patients, originating from post-ligation oesophageal ulcer in one patient and portal-hypertensive gastropathy in two, all of whom could be well controlled. No case of heparin-induced thrombocytopenia was observed in these series, and no other treatment-related

untoward effects were noticed. The impact of portal vein thrombosis or its recanalisation on the course of the disease was not assessed. Factors predicting recanalisation were a partially occluding thrombus and a prolongation of anticoagulation after partial response. Overall, these data suggest a favourable benefit: risk ratio for anticoagulation in cirrhotic patients with portal vein thrombosis.

TIPS as an alternative to anticoagulation for portal vein thrombosis Experience with TIPS in patients with portal vein thrombosis is growing [104–109]. In most of the patients, TIPS was indicated for the treatment of refractory complications of liver disease. Most studies included patients with partial or complete occlusive thrombi and patients with cavernoma. TIPS insertion was usually associated with mechanical fragmentation and aspiration of the thrombus and, frequently, anticoagulation. TIPS insertion was successful in all or in > 90% of the patients with partial or complete occlusive thrombi, respectively, and in about 70% of those with cavernoma. The main risk factors predicting failure of insertion were partial occlusive thrombosis and the absence of visible intrahepatic portal veins, but not the presence of cavernoma when such veins were visible. Complications and mortality rates were similar in patients with or without portal vein thrombosis [109].

Anticoagulation for primary prevention of portal-vein thrombosis LMWH administered for 1 year subcutaneously at prophylactic dosage prevented the development of thrombosis as well as the occurrence of disease decompensation in a randomised controlled study without significant association with bleeding [110].

Other use of anticoagulation in cirrhosis A prospective observational study included 75 patients with cirrhosis for whom there was an indication for thromboprophylaxis with LMWH. Five patients developed bleeding complications, none of which were lethal. There was no relationship between bleeding episodes and anti-FXa activity measurement in plasma [111].

Monitoring anticoagulation in cirrhosis Conventional INR is unreliable in cirrhosis [112] and the anti-FXa activity measured in non-anticoagulated patients is negatively correlated with the severity of liver disease and positively with antithrombin levels [111]. Therefore, monitoring VKA and LMWH in patients with cirrhosis remains a challenge.

Conclusions

CLD, until recently considered as the prototype acquired coagulopathy responsible for bleeding, should now be regarded as a condition associated with normal or increased thrombin generation, and the bleeding events that occur in these patients should be explained by the superimposed conditions that frequently occur in this setting. Because of increased FVIII (procoagulant driver) combined with decreased PC (anticoagulant driver), a procoagulant imbalance, defined as a partial resistance to the *in vitro* anticoagulant action of thrombomodulin, can be demonstrated in CLD. This hypercoagulability may be responsible for the observed increased risk of VTE shown by epidemiological studies, and for the progression of liver fibrosis as shown by the evidence that VKA or LMWH are able to slow down hepatic fibrosis.

Although apparently provocative, considering anticoagulation as a therapeutic option in patients with cirrhosis is now supported by a rationale of increasing strength. LMWH and/or VKA are the drugs currently available. Both are indirect antithrombotic drugs: LMWH requires antithrombin (critically reduced in some patients) and VKA (together with the vitamin-K-dependent pro-coagulants) do further decrease the anticoagulants PC and protein S that are already considerably low before the initiation of therapy. Perhaps, VKA and LMWH are not the ideal drugs in cirrhosis. In contrast, the new antithrombotic drugs because of their direct action on FXa or thrombin may be a better option, and warrant investigation. However, much remains to be done to identify subgroups of patients who may benefit from anticoagulation to treat or prevent thrombosis and to slow down hepatic fibrosis.

Addendum

The authors contributed to this review article as follows: A. Tripodi Conceived the article. Drafted the introduction, the sections on hypercoagulability and conclusions. Assembled and revised the manuscript. Q. M. Anstee Drafted the section on hepatic fibrogenesis and revised the manuscript. K. K. Sogaard Drafted the section on the risk of venous thromboembolism and revised the manuscript. M. Primignani Helped drafting the section on hypercoagulability and revised the manuscript. D. C. Valla Drafted the section on anticoagulation in cirrhosis and revised the manuscript.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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