Cirrhosis as a risk factor for venous thrombosis

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Chronic and acute liver diseases have long been considered as the epitome of acquired bleeding disorders. Evidence in support of this included profoundly abnormal test results of routine diagnostic tests of haemostasis in combination with clinical bleeding (1). Although bleeding in patients with cirrhosis is common, many of the clinically relevant bleeding episodes – i.e. variceal bleeds – are unrelated to haemostasis. These bleeding events are rather a consequence of portal hypertension and local vascular abnormalities (2).

Laboratory studies performed in the last decade have provided evidence for a rebalanced haemostatic system in patients with liver diseases (3, 4). This new haemostatic balance is a consequence of a simultaneous decline in pro- and anti-haemostatic drivers (►Figure 1). The haemostatic balance in patients with liver disease is, however, unstable and can display both hypo- and hypercoagulable features. Hypocoagulable features include decreased clot formation and stability in some studies using viscoelastic testing (5), hyperfibrinolysis (6), and delayed fibrin polymerisation (7). Hypercoagulable features include platelet hyperreactivity which appears related to endotoxaemia (8, 9), enhanced thrombin generating potential (10), increased production of intravascular tissue factor (11), and a prothrombotic fibrin structure (12).

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The unstable haemostatic balance in cirrhosis is thought to contribute to bleeding or thrombotic events although it remains difficult to predict which patient is at risk for bleeding or thrombosis. The hypercoagulable features in patients with cirrhosis have only been recognised in recent years, and it has also only been recently acknowledged that patients with cirrhosis are not protected from clinical thrombotic events.

In 2006, Northup et al. were the first to report on the incidence of venous thrombosis in hospitalised patients with cirrhosis, and this group concluded that despite prolongations in the international normalised ratio (INR) and use of thromboprophylaxis in some patients venous thrombotic events did occur (13). Subsequent studies even suggested that liver disease was in fact a risk factor for development of venous thrombosis (14). An increased risk of venous thrombosis in cirrhosis could be related to the hypercoagulable features discussed in the previous paragraph, but may also relate to endothelial dysfunction (a common feature in cirrhosis) (15, 16), or stasis (either related to the hyperdynamic circulation or to reduced mobility of the sicker patient with cirrhosis).

In this issue of *Thrombosis and Haemostasis*, Ambrosino et al. report a systematic review and meta-analysis of the risk of venous thrombosis in patients with cirrhosis (17). Using a dataset of nearly 700,000 patients with cirrhosis and nearly 1.5 million controls from 11 studies, the authors demonstrate an overall 1.7-fold increased risk of venous thrombosis in patients with cirrhosis, with similar estimates when deep-vein thrombosis and pulmonary embolism were considered individually. Interestingly, males with cirrhosis appeared to have an increased risk for venous thrombosis compared to females.

While acknowledging the limitations of systematic reviews and meta-analyses (18), we do think the data by Ambrosino et al. are important as they have important clinical consequences. The fact that cirrhosis is a risk factor for venous thrombosis reinforces the notion that routine thromboprophylaxis should not be withheld despite prolongations in the INR (19). Recent retrospective studies have suggested that thromboprophylaxis does not reduce the rate of venous thrombosis in patients with cirrhosis (20–22). Nevertheless, thromboprophylaxis, in particular with low-molecular-weight heparin (LMWH), appears safe in terms of bleeding risk (20–23). These results might be explained by the fact that many patients in these studies were at low risk for venous thrombosis, by cautious use of thromboprophylaxis (e.g. dose-adjustments in those patients with prolonged INRs), or by decreased anticoagulant effects of heparins due to decreased plasma levels of antithrombin. Routine thromboprophylaxis with heparins in patients with cirrhosis can be complicated by issues with dosing and monitoring. It has been shown that anticoagulant drugs have altered potency in patients with cirrhosis, at least *in vitro* (24). Importantly, monitoring tests of heparins are unreliable in patients with cirrhosis, anti-Xa tests underestimate, and APTT-based testing overestimates heparin levels (25). Prospective clinical studies on efficacy and safety of thromboprophylaxis in patients with cirrhosis are therefore urgently required. Patients in such studies may be stratified according to their risk of thrombotic events. The Padua risk prediction score has been demonstrated to predict thrombosis risk also in patients with cirrhosis (22, 26).

The new generation non-vitamin K antagonist oral anticoagulant drugs (NOACs, also referred to as Direct Oral Anticoagulants or DOACs (27)) may have benefits over LMWH in patients with cirrhosis (28). One of the advantages of NOACs in

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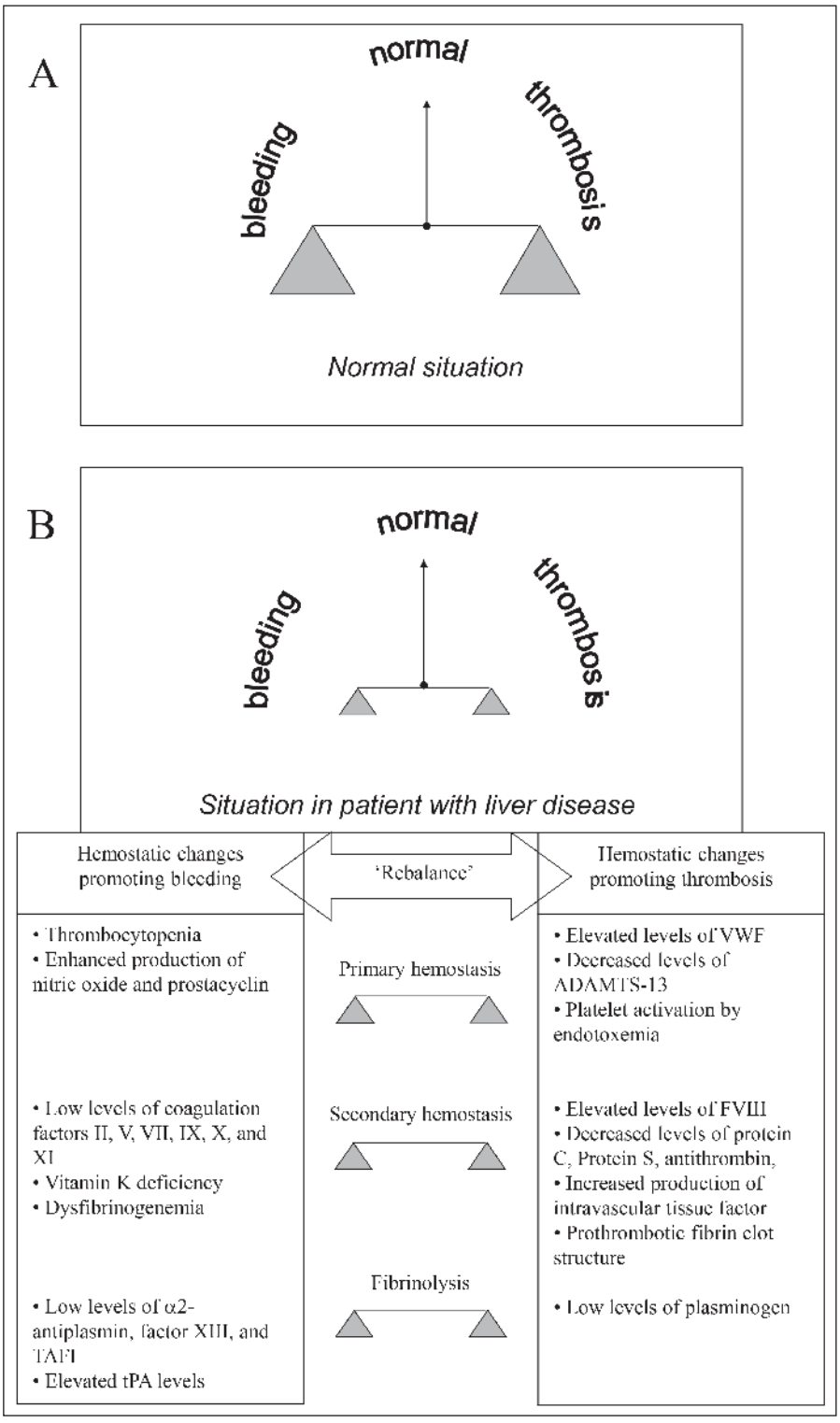

Figure 1: Rebalanced haemostasis in patients with liver disease. In healthy persons (A), haemostasis is in a solid balance. In patients with liver disease (B and table), concomitant changes in pro- and antihemostatic pathways result in a "rebalance" in the haemostatic system. Rebalance in the haemostatic system occurs at the level of primary and secondary haemostasis, and in the fibrinolytic system. This new balance, however, presumably is less stable compared with the balance in healthy volunteers, and may thus more easily tip toward either bleeding or thrombosis. Modified from Warnaar et al. [36] with permission from Wolters Kluwer Health.

patients with cirrhosis is their independence of antithrombin levels, which may be a contributor to a decreased effect of heparins in these patients. However, there is very little clinical experience with NOACs in patients with liver disease, and NOACs are not recommended for patients with (advanced) cirrhosis according to their package inserts. In addition, the *in vitro* anticoagulant effects of NOACs are profoundly altered in patients with cirrhosis (24, 29). Nevertheless, limited clinical experience suggests NOACs are probably safe in patients with mild to moderate cirrhosis, even when used long-term (30–32).

Besides prophylaxis using anticoagulant therapy, a more aggressive approach to combat endotoxaemia may be effective in reducing the risk of venous thrombosis. It has been well established that endotoxaemia results in a procoagulant state. In patients with cirrhosis, endotoxaemia is thought to contribute to endothelial cell activation (15), tissue factor expression (11) followed by activation of coagulation (33, 34), and stimulation of platelet function (8), which all may favour development of venous thrombosis. Antibiotic therapy may thus also reduce the risk for venous thrombosis, and this strategy requires clinical validation, perhaps only in high-risk patients. Interestingly, antibiotics have also been shown to reduce variceal (re)bleeding and improve haemostatic status (35), so an antithrombotic strategy using antibiotics may "hit two birds with one stone".

In aggregate, the systematic review by Ambrosino et al. in this issue of *Thrombosis and Haemostasis* reaffirms that patients with cirrhosis are at risk for development of venous thrombosis. Thromboprophylactic therapy is thus indicated in these patients, despite routine diagnostic tests of haemostasis suggests these patients to be 'auto-anticoagulated'. Clinical studies on optimal thromboprophylactic strategies in these patients that frequently have profound haemostatic alterations are urgently required.

Conflicts of interest
None declared.

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