Review

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

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Summary

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

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

Introduction

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

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

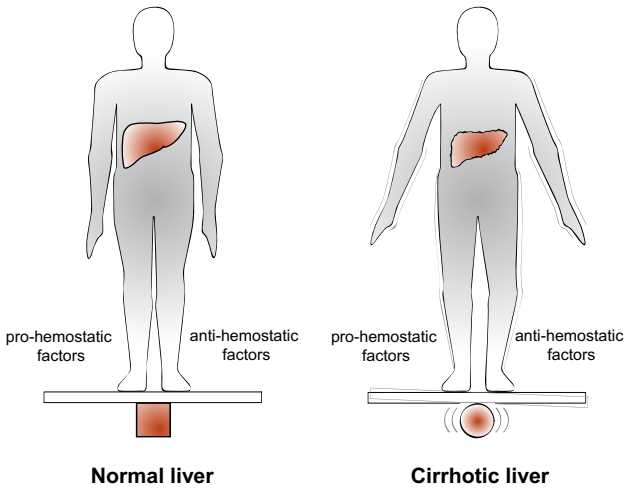

Fig. 1. The hemostatic balance in patients with liver disease as compared to that of healthy individuals. This cartoon depicts the stable hemostatic balance in healthy individuals and shows that although the hemostatic system in patients with liver disease is (re)balanced, the balance is fragile and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

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

Thrombotic diseases in patients with cirrhosis

Portal vein thrombosis

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

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

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

Venous thrombosis

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

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

Arterial thrombosis

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

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