

## Preface

**Hemostatic Dysfunction in Liver Diseases**Ton Lisman, PhD<sup>1</sup> Hau C. Kwaan, MD, FRCP<sup>2</sup>

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The liver plays a central role in hemostasis, as it is the site of synthesis of most procoagulant and anticoagulant factors. It also synthesizes many fibrinolytic proteins, and is an important source of thrombopoietin. Furthermore, it is involved in clearance of many hemostatic and fibrinolytic components. Consequently, patients with a decreased synthetic capacity of the liver acquire a complex coagulopathy, with decreased plasma levels of hepatocyte-derived hemostatic proteins and a decreased platelet count.<sup>1</sup> In addition, chronic and acute liver diseases are characterized by chronic endothelial cell activation resulting in additional hemostatic changes such as substantially elevated plasma levels of von Willebrand factor (VWF).<sup>2,3</sup> Finally, systemic or intrahepatic activation of coagulation results in consumption of platelets and hemostatic proteins.<sup>4,5</sup>

These hemostatic changes accompanying liver diseases are among the most complex acquired hemostatic changes, and the net effects of these changes have, therefore, long been unclear. Historically, patients with liver diseases were considered to have a significant bleeding risk. This belief arose primarily from observations of prolonged coagulation screening test results, especially the prothrombin time/international normalized ratio (PT/INR), the apparent reduction of many liver-derived coagulation factors (e.g., II, V, VII, IX, X, and XI), and reduction in platelet count, leading to a perceived “hypocoagulable” state. Careful clinical observation and extensive laboratory studies, however, have led to the concept of a rebalanced hemostasis.<sup>6</sup> The notion that the hemostatic balance in liver disease is reset because of a concomitant decline in both prohemostatic (as noted earlier) and anti-hemostatic (e.g., proteins C and S) components and consequent processes is therefore rapidly gaining acceptance.<sup>7,8</sup> Furthermore, it is increasingly recognized that the hemostatic status of patients with liver disease comprises hypercoagulable components (e.g., increases in VWF, factor VIII, and decreases in anticoagulant proteins).<sup>9–12</sup> These hypercoagulable features explain, at least partly, why systemic and local

thrombotic events in patients with liver diseases are common.<sup>13,14</sup>

In total, the hemostatic balance in liver disease appears more fragile compared with that of healthy individuals, and this explains why both bleeding and thrombotic complications can occur in these patients. The current clinical challenges include the prediction and management of bleeding and thrombotic events in patients with both chronic and acute liver diseases. Thus, we have assembled in this issue of *Seminars in Thrombosis and Hemostasis* several articles on the pathophysiology and clinical management of the coagulopathy of liver diseases by prominent investigators in this field, and thus providing our readers with updated information on this important clinical field.

To begin, Hoffman outlines the central role of the liver in hemostasis, citing the concept of the cell-based hemostasis model to show the limited value of common tests such as the PT.<sup>15</sup> Next, Giannini and Peck-Radosavljevic discuss how thrombopoietin with thrombocytopenia may be affected in the different liver diseases.<sup>16</sup> This is followed by an article by Tripodi and Mannucci who describe the imbalance between the procoagulant and anticoagulant effects in the chronic liver diseases.<sup>17</sup> Lisman and Stravitz then discuss hemostatic changes in patients with acute liver failure, which are similar, but not identical to the changes in patients with cirrhosis, and provide evidence for hemostatic rebalance in this particular type of liver disease.<sup>18</sup> Excessive fibrinolysis, another major abnormality in liver dysfunction, is then reviewed by Leebeek and Rijken, who present findings of hyperfibrinolysis in various liver diseases and provide critical analysis of different laboratory tests for fibrinolytic activity.<sup>19</sup> Barrera et al then show the link between hemostatic alterations and the risk for variceal bleeding in patients with cirrhosis.<sup>20</sup>

The increased risk for cardiovascular events in patients with diabetes, obesity, and the metabolic syndrome have been well established, and the increased risk has been partly ascribed to prohemostatic changes. However, less is known

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on the hemostatic changes in patients with nonalcoholic fatty liver disease (NAFLD), particularly, when it has advanced to cirrhosis. Potze et al discuss the incidence and risk factors for vascular disease in NAFLD and explore the potential role of hemostatic changes therein.<sup>21</sup> Valla then outlines risk factors, diagnosis, and treatment of splanchnic vein thrombosis,<sup>22</sup> after which Derman and Kwaan provide additional data from their single institutional findings.<sup>23</sup> Intagliata and Northup then discuss opportunities and pitfalls for prevention and treatment of thrombotic disease in patients with liver diseases using anticoagulant therapy.<sup>24</sup> A pragmatic approach to prevention and treatment of bleeding and thrombosis in critically ill patients with liver disease is then provided by Roberts and Bernal,<sup>25</sup> and Mallett subsequently outlines how viscoelastic tests of coagulation help in management decisions on bleeding and thrombosis in patients with liver disease and during liver transplantation.<sup>26</sup> Finally, Massicotte et al present data from their institution which uses state-of-the-art approaches to prevention of blood loss during liver transplantation.<sup>27</sup>

In total, the contributions to this issue of *Seminars in Thrombosis and Hemostasis* amply illustrate that the field of coagulopathy in liver diseases has been rapidly evolving over the last decade, with novel concepts that truly impact on our understanding of this disorder and on the clinical consequences that are changing the way we are managing patients with liver disease. We trust that our readers will be as excited to be updated with this remarkable progress as we are.

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