Preface

Platelet Function in Thrombosis and Hemostasis

Anne-Mette Hvas, MD, PhD[1]

[1] Department of Clinical Biochemistry, Centre for Hemophilia and Thrombosis, Aarhus University Hospital, Aarhus N, Denmark

Semin Thromb Hemost 2016;42:183–184.

Platelets represent the main effectors in the formation of the initial hemostatic plug through an elaborate response to vascular injury, and furthermore, platelets play an essential role in secondary hemostasis.[1] However, platelets are also important contributors to pathological thrombus formation and vessel occlusion when activated inappropriately. Moreover, platelets contribute to processes beyond hemostasis and thrombosis such as inflammation, wound healing, and maintenance of vascular integrity.[2]

In the present issue of *Seminars in Thrombosis & Hemostasis*, the focus is on the physiology of platelets as well as diagnostic issues, both as regard to bleeding disorders and thromboembolic risk. In a series of articles, the issue provides an overview of some of the main conditions influencing platelet function and of different diagnostic approaches to investigating platelet function. The role of platelets in cardiovascular disease and venous thromboembolism and the effect of antiplatelet drugs are reviewed and discussed in another series of articles.

First, Lassila introduces the reader to the overall role of platelets as well as issues to consider when testing platelet function in bleeding disorders.[3] Following this introduction, Gremmel et al provide a comprehensive review on platelet physiology, with particular focus on structure, granules, surface glycoproteins, and activation pathways.[4] The authors illustrate how new imaging techniques have improved the knowledge on platelet structure, secretion, adhesion, and activation, and how these techniques have expanded our understanding of the role of platelets in health and disease.

Recent research has revealed platelets as more active components of the immune system besides the previously considered passive immune-modulatory role. Through a cross-talk with the immune system, platelets have emerged as both critical modulators of atherothrombosis and vascular inflammation and as effector cells in the combat of microbial infection. Chatterjee and Geisler provide an overview of the complex area of platelet-derived targets involved in inflammatory pathways and platelets as regulator of the immune system.[5]

Although platelets are anucleate cells, they retain many of the RNA metabolic processes of nucleated cells. Lindsay and Edelstein outline the current knowledge as regard to platelets and microRNA, and the possible role for platelet function in disease and in the regulation of platelet physiology.[6]

The subsequent section contains reviews on the role of platelets in several disease entities. First, Pasalic et al discuss biomarkers of cardiovascular disease with focus on the role of platelets.[7] They also provide a comprehensive review presenting the significance of measures of platelet activity and platelet aggregation as risk markers of cardiovascular disease. Several methods of platelet function testing have been evaluated for these conditions, but these data remain conflicting, and platelet biomarkers have not been widely incorporated in cardiovascular risk scores so far.

The risk of cardiovascular disease among patients with type 2 diabetes mellitus has attracted increased attention during the recent decades. The significance is underlined by the fact that patients with prediabetes also have an increased risk of cardiovascular events.[8] Therefore, Neergaard-Petersen et al summarize current knowledge on the potential cardiovascular role of platelets in patients with diabetes.[9] This review also provides an updated status on the benefits and limitations of antiplatelet therapy in diabetic patients with cardiovascular disease.

As regard to thromboembolic disease, platelets have been ascribed far more significance in arterial cardiovascular disease than in venous thromboembolic disease. Montoro-García et al present recent evidence suggesting that platelets may play a more important role in venous thromboembolism than previously anticipated.[10] This review also discusses the potential applications of platelets as novel risk factors for venous thromboembolic disease. The authors additionally point to future important issues, such as whether the contribution of platelet-associated risk factors is dependent on

Address for correspondence Anne-Mette Hvas, MD, PhD, Department of Clinical Biochemistry, Centre for Hemophilia and Thrombosis, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, DK - 8200 Aarhus N, Denmark (e-mail: am.hvas@dadlnet.dk).

Issue Theme Platelet Function in Thrombosis and Hemostasis; Guest Editor: Anne-Mette Hvas, MD, PhD.

DOI http://dx.doi.org/10.1055/s-0036-1572329.
ISSN 0094-6176.

specific clinical conditions and whether these risk factors *reflect* or *cause* the prothrombotic situation.

In patients with critical illness, thrombocytopenia may be an indicator of various serious disorders. Levi reviews the epidemiology and the various causes of thrombocytopenia in critically ill patients.[11] The most frequently occurring diagnoses are summarized with a special attention paid to the significance of platelets in sepsis (with or without disseminated intravascular coagulation), the platelet–vessel wall interaction as well as the role of ADAMTS13 in critical illness. This review points to the importance of considering relevant differential diagnoses and making a correct diagnosis for thrombocytopenia in critically ill patients, as this is essential to provide adequate and timely treatment of these patients.

The third section of the present issue of *Seminars in Thrombosis & Hemostasis* reviews and discusses the challenges in diagnostic approaches to investigation of platelet disorders and evaluation of antiplatelet drugs.

During the past decades, a range of whole blood platelet function tests has been developed as an alternative to light transmittance aggregometry, which historically has been considered the gold standard. Lordkipanidzé presents on the variety of different platelet function tests and discusses advantages and drawbacks of the different tests.[12] This review also discusses important issues to be taken into account when interpreting platelet function test results, including preanalytical variables.

Recently, increasing attention has been paid to flow cytometry for evaluation of platelet function. Ramström et al present the current status and describe factors to consider in flow cytometry for platelet function testing.[13] The authors also discuss the possibilities and challenges for future use of flow cytometry in clinical settings. A further example is then presented by Cai et al, who report the usefulness of flow cytometric mepacrine uptake and release combined with a CD63 assay in the diagnosis of patients with suspected platelet dense granule disorder.[14]

Inherited platelet disorders are a diagnostic challenge, due to the clinical heterogeneity of these disorders. Moreover, agreement about the classification of inherited platelet disorders has not been achieved and the standardization of laboratory tests used for their investigation is inadequate. Gresele et al meet this challenge and provide algorithms outlining the steps in diagnosis of inherited platelet disorders.[15]

Although the antithrombotic properties of platelet inhibitors are widely accepted, several studies have questioned their effect in many cardiovascular patients, and there is an intensive debate on the predictive value of platelet function testing, both in the evaluation of the effect of platelet inhibitors and in prediction of bleeding risk. Gross et al present the current evidence on the prognostic value of platelet function testing regarding ischemic events with focus on patients undergoing percutaneous coronary intervention and concerning platelet function testing in the prediction of bleeding events.[16] Furthermore, the authors discuss the possible future role of platelet function testing for individualized antiplatelet treatment regimens in high-risk patients.

Platelets play a pivotal role in both hemostasis and thrombosis. An adequate diagnostic approach is essential in cases of bleeding tendency and when a platelet disorder is suspected. The role of platelets in thromboembolic disease and the mechanisms behind a reduced antiplatelet effect need further investigation. A prerequisite for the diagnostic workup is standardized laboratory analysis and knowledge on the strengths and weaknesses of the methods. We hope that this issue of *Seminars in Thrombosis & Hemostasis* will provide a most useful and interesting update on these platelet-related issues.

References

1 Hoffman M, Monroe DM III. A cell-based model of hemostasis. Thromb Haemost 2001;85(6):958–965
2 Smyth SS, McEver RP, Weyrich AS, et al; 2009 Platelet Colloquium Participants. Platelet functions beyond hemostasis. J Thromb Haemost 2009;7(11):1759–1766
3 Lassila R. Platelet function tests in bleeding disorders. Semin Thromb Hemost 2016;42(3):185–190
4 Gremmel T, Frelinger AL III, Michelson AD. Platelet physiology. Semin Thromb Hemost 2016;42(3):191–204
5 Chatterjee M, Geisler T. Inflammatory contribution of platelets revisited: new players in the arena of inflammation. Semin Thromb Hemost 2016;42(3):205–214
6 Lindsay CR, Edelstein LC. MicroRNAs in platelet physiology and function. Semin Thromb Hemost 2016;42(3):215–222
7 Pasalic L, Wang S, Chen VMY. Platelets as biomarkers of coronary artery disease. Semin Thromb Hemost 2016;42(3):223–233
8 DeFronzo RA, Abdul-Ghani M. Assessment and treatment of cardiovascular risk in prediabetes: impaired glucose tolerance and impaired fasting glucose. Am J Cardiol 2011;108(3, Suppl): 3B–24B
9 Neergaard-Petersen S, Hvas AM, Kristensen SD, Grove EL. Platelets and antiplatelet therapy in patients with coronary artery disease and diabetes. Semin Thromb Hemost 2016;42(3):234–241
10 Montoro-García S, Schindewolf M, Stanford S, Larsen OH, Thiele T. The role of platelets in venous thromboembolism. Semin Thromb Hemost 2016;42(3):242–251
11 Levi M. Platelets in critical illness. Semin Thromb Hemost 2016; 42(3):252–257
12 Lordkipanidzé M. Platelet function tests. Semin Thromb Hemost 2016;42(3):258–267
13 Ramström S, Södergren AL, Tynngård N, Lindahl TL. Platelet function determined by flow cytometry: new perspectives? Semin Thromb Hemost 2016;42(3):268–281
14 Cai H, Mullier F, Frotscher B, et al. Usefulness of flow cytometric mepacrine uptake/release combined with CD63 assay in diagnosis of patients with suspected platelet dense granule disorder. Semin Thromb Hemost 2016;42(3):282–291
15 Gresele P, Bury L, Falcinelli E. Inherited platelet function disorders: algorithms for phenotypic and genetic investigation. Semin Thromb Hemost 2016;42(3):292–305
16 Gross L, Aradi D, Sibbing D. Platelet function testing in patients on antiplatelet medications. Semin Thromb Hemost 2016;42(3): 306–320