Preface

Editorial Compilation X

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Welcome to the latest issue of *Seminars in Thrombosis and Hemostasis (STH)* published under the "banner" of "Editorial Compilation," this being the tenth such issue. Although *STH* is historically a theme-driven publication, ongoing opportunities arise to publish compilations containing wide-ranging contributions of current interest and controversy, and which do not quite match a current themed issue in progress. We also require a medium to enable publication of unsolicited manuscripts as well as contributions from our Eberhard F. Mammen Young Investigator Award winners (►**Table 1**). As is now standard for this compilation series, the current issue has a mixture of content that comprises the above elements, as well as broadly fitting within the standard themes of "thrombosis" and "bleeding."

This issue begins with a contribution from Larsen and Hvas, on the topic of thrombin.[1] This contribution was commissioned since thrombin is a topic of particular interest to our readership, and a relatively old publication on thrombin[2] kept appearing on our annual most popular lists,[3] indicating it was time to update the "thrombin story" for our readership. Thrombin is a serine protease and a naturally derived enzyme that plays a key role in hemostasis by converting fibrinogen to fibrin and activating coagulation factor XIII whereby the fibrin clot is stabilized. Furthermore, thrombin activates platelets through protease-activated receptors on the platelet surface. Conversely, thrombin also exerts anticoagulant effects, enhancing protein C activity while complexed with the endothelial protein thrombomodulin. During recent years, it has become evident that thrombin has significant effects also beyond hemostasis, as it contributes also to the modulation of endothelium, promotes inflammation and angiogenesis, and plays a role in tumor progression. However, due to the very short half-life and almost immediate inhibition in fluid-phase by its natural inhibitor antithrombin, thrombin itself remains elusive, and only indirect measurements of thrombin are reliably feasible. This review provides a description of structure and mechanisms of action of thrombin both in physiological and pathological processes. Furthermore, it summarizes laboratory tests that measure in vivo or ex vivo thrombin generation and presents knowledge on the value of these biomarkers in bleeding disorders, cardiopulmonary by-pass surgery, and thromboembolic risk assessment in different patient populations. Finally, the review outlines further perspectives on using thrombin generation biomarkers for research purposes and clinical practice.

This issue of STH continues with the exploration of fibrin network porosity and endo-/exogenous thrombin crosstalk from a contribution from He et al.[4] The earliest assessment of fibrin network porosity used a liquid permeation system and confocal three-dimensional microscopy, which was later replaced by scanning electron microscopy. Although the methods have extensively been applied in studies of health or disease, there remains debate on the choice of a proper clotting trigger. In this review, the authors assess published data and convey their opinions with regard to several issues. First, when the coagulation process is initiated by recombinant tissue factor (rTF) and phospholipids, the fibrin network porosity is regulated by the endogenous thrombin based on enzymatic activations of multiple coagulants. If purified thrombin (1.0 IU/mL) is employed as the clotting trigger, fibrin network porosity may be affected by exogenous thrombin, which directly polymerizes fibrinogen in plasma, and additionally by endogenous thrombin stemming from a "positive feedback loop" action of the added thrombin. Second, with use of either endogenous or exogenous thrombin, the concentration and clotting property of available fibrinogen both influence fibrin network porosity. Third, in the assay systems in vitro, exogenous thrombin but not rTF-induced endogenous thrombin seems to be functional

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Table 1 Past STH editorials related to Eberhard F. Mammen award announcements

1. Favaloro EJ. Welcome to a special issue of seminars in thrombosis and hemostasis—the closing issue for 2008. Semin Thromb Hemost 2008;34:693–696
2. Favaloro EJ. A tribute to Eberhard F. Mammen, M.D. (1930-2008). Semin Thromb Hemost 2008;34(8):703–707
3. Favaloro EJ. Welcome to the first issue of Seminars in Thrombosis and Hemostasis for 2009. Semin Thromb Hemost 2009;35:1–2
4. Favaloro EJ. Winners of the Inaugural Eberhard F. Mammen Award for Most Popular Article. Semin Thromb Hemost 2009;35:587–590
5. Favaloro EJ. Editorial. 2009 Eberhard F. Mammen Young Investigator Award Winners. Semin Thromb Hemost 2010;36:469–470
6. Favaloro EJ. Winners of the 2010 Eberhard F. Mammen award for most popular article during 2008-2009. Semin Thromb Hemost 2010;36(7):685–692
7. Favaloro EJ. 2011 Eberhard F. Mammen award announcements. Semin Thromb Hemost 2011;37(5):431–439
8. Favaloro EJ. 2012 Eberhard F. Mammen award announcements. Semin Thromb Hemost 2012;38:425–432
9. Favaloro EJ. Eberhard F. Mammen award announcements. Semin Thromb Hemost 2013;39:567–574
10. Favaloro EJ. 2014 Eberhard F. Mammen award announcements: Part I—most popular articles. Semin Thromb Hemost 2014;40(4):407–412
11. Favaloro EJ. 2014 Eberhard F. Mammen award announcements: Part II-Young Investigator Awards. Semin Thromb Hemost 2014;40(7):718–723
12. Favaloro EJ. 2015 Eberhard F. Mammen Award Announcements: Part I—Most Popular Articles. Semin Thromb Hemost 2015;41(7):673–679
13. Favaloro EJ. 2015 Eberhard F. Mammen Award announcements: Part II-Young Investigator Awards. Semin Thromb Hemost 2015;41(8):809–815
14. Favaloro EJ. 2016 Eberhard F. Mammen Award Announcements: Part I—Most Popular Articles. Semin Thromb Hemost 2016;42(4):325–330
15. Favaloro EJ. 2016 Eberhard F. Mammen Award Announcements: Part II-Young Investigator Awards. Semin Thromb Hemost 2017;43(3):235–241
16. Favaloro EJ. 2017 Eberhard F. Mammen Award Announcements: Part I-Most Popular Articles. Semin Thromb Hemost 2017;43 (4):357–363
17. Favaloro EJ. 2017 Eberhard F. Mammen Award Announcements: Part II-Young Investigator Awards. Semin Thromb Hemost 2018;44(2):81–88
18. Favaloro EJ. 2018 Eberhard F. Mammen Award Announcements: Part I-Most Popular Articles. Semin Thromb Hemost 2018;44 (3):185–192
19. Favaloro EJ. 2018 Eberhard F. Mammen Award Announcements: Part II-Young Investigator Awards. Semin Thromb Hemost 2019;45(2):123–129
20. Favaloro EJ. 2019 Eberhard F. Mammen Award Announcements: Part I-Most Popular Articles. Semin Thromb Hemost 2019;45 (3):215–224
21. Favaloro EJ. 2019 Eberhard F. Mammen Award Announcements: Part II—Young Investigator Awards. Semin Thromb Hemost 2020;46(2):105–113
22. Favaloro EJ. 2020 Eberhard F. Mammen Award Announcements: Part I-Most Popular Articles. Semin Thromb Hemost 2020;46 (4):383–392
23. Favaloro EJ. 2020 Eberhard F. Mammen Award Announcements: Part II—Young Investigator Awards. Semin Thromb Hemost 2021;47(3):229–237
24. Favaloro EJ. 2021 Eberhard F. Mammen Award Announcements: Part I-Most Popular Articles. Semin Thromb Hemost; 2021: 47(5):467–476

enough to activate Factor XIII, which then contributes to a decrease in the fibrin network porosity. Fourth, fibrin network porosity determines the transport of fibrinolytic components into/through the clots, thus serving as an indicator of the fibrinolysis potential in plasma.

Next is a contribution around the topic of antiphospholipid syndrome (APS) by Álvarez and colleagues,[5] and specifically looking at microparticles as an alternative explanation to the behavior of vascular APS. APS is an autoimmune disease characterized by persistent presence of antiphospholipid antibodies (aPL), along with the occurrence of vascular thrombosis and pregnancy morbidity. The variety of aPL and their related mechanisms, as well as the behavior of disease in wide groups of patients, have led some authors to propose a differentiation of this syndrome into two independent entities: vascular and obstetric APS. Thus,

previous publications have discussed whether specific autoantibodies may be responsible for this differentiation, or in contrast, how the same antibodies are able to generate two different clinical presentations. This discussion is yet to be settled. The capability of serum IgG from patients with vascular thrombosis to trigger the biogenesis of endothelial cell-derived microparticles in vitro is one described difference between the clinical entities of APS. These vesicles constitute a prothrombotic mechanism since they can directly lead to clot activation in murine models and recalcified human plasma. Nevertheless, other indirect mechanisms by which microparticles can spread a procoagulant phenotype could be critical to understanding their role in APS. For this reason, questions regarding the cargo of microparticles, and the signaling pathways involved in their biogenesis, are of interest in attempting to explain the behavior of this autoimmune disease.

Next in this issue is a review on the contemporary clinical use of aspirin, its mechanisms of action, current concepts, unresolved questions, and future perspectives, by Christiansen and colleagues.[6] This represents another commissioned work, for similar reasons expressed previously for thrombin, with an old aspirin paper[7] on the most popular listing in STH.[3] Thus, aspirin, as a topic of interest, has previously been well evidenced by our readership. The ability of aspirin to inhibit platelet aggregation has positioned this agent within the most frequently used drugs worldwide. Results from several clinical trials have led to strong guideline recommendations for aspirin use in acute management and secondary prevention of cardiovascular disease. On the contrary, guidelines regarding aspirin use as primary prevention of cardiovascular disease are almost conservative, supported by recent trials reporting that the bleeding risk may outweigh the potential benefits in most patients. In pregnancy, aspirin has proven efficient in preventing preeclampsia and small-for-gestational-age births in women at high risk and hence is widely recommended in clinical guidelines. Despite the vast amount of clinical data on aspirin, several unresolved questions remain. Randomized trials have reported that aspirin reduces the risk of recurrent venous thromboembolism, but the clinical relevance remains limited, because direct oral anticoagulants (DOACs) are more effective. Laboratory studies suggest that a twice daily dosing regimen or evening intake may lead to more efficient platelet inhibition, and the potential clinical benefit of such strategies is currently being explored in ongoing clinical trials. Enteric-coated formulations of aspirin are frequently used, but it remains unclear if they are safer and as efficient as plain aspirin. In the future, aspirin use after percutaneous coronary interventions might not be mandatory in patients who also need anticoagulant therapy, as several trials support shorter aspirin duration strategies. On the other hand, new treatment indications for aspirin will likely arise, as there is growing evidence that this widespread drug may reduce the risk of colorectal malignancies and other types of cancer.

Next, is a review by Korpallová and colleagues, on rotational elastometry (ROTEM) testing for DOACs.[8] These drugs are increasingly used worldwide for prevention of stroke in patients with atrial fibrillation and to prevent or treat venous thromboembolism. In situations such as serious bleeding, the need for urgent surgery/intervention or management of a thromboembolic event, the laboratory measurement of DOACs levels, or anticoagulant activity may be required. ROTEM represents a viscoelastic hemostatic assay that has been used in emergencies (trauma and obstetrics), and surgical procedures (cardiac surgery and liver transplants), but experience with this assay in DOAC-treated patients is still limited. Therefore, this article aims to review the use of ROTEM in the setting of DOAC therapy, focusing on DOAC-associated bleeding and the use of this instrument for the management of reversal strategies for DOAC-associated anticoagulation.

Next is a review on anti-Xa monitoring of low-molecular weight heparin (LMWH) during pregnancy, by Kjaergaard et al.[9] LMWH is commonly used for preventing or treating venous thromboembolic disease (VTE) during pregnancy. The physiological changes in maternal metabolism have led to discussions on optimal LMWH dosing strategy and possible need for monitoring. The aim of this systematic review is to summarize and discuss whether LMWH dose adjustment according to anti-Xa provides superior effectiveness and safety compared with weight-adjusted or fixed-dosed LMWH in pregnant women. A systematic literature search was performed in Pubmed, Embase, and Scopus. The study is reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Effectiveness was defined as episodes of thrombosis and safety as bleeding episodes. In total, 33 studies were included: four randomized controlled studies and 29 cohort studies. Prophylactic dosing strategies employing weight-dosed, fixed-dosed, or anti-Xa adjusted LMWH dosing performed identically in effectiveness and safety. In pregnant women with VTE or high thromboembolic risk, therapeutic weight-adjusted LMWH and weight-plus anti-Xa adjusted LMWH provided equal results in terms of effectiveness and safety. Pregnant women with mechanical heart valves (MHVs) received therapeutic anti-Xa adjusted LMWH with four out of seven studies presenting mean peak anti-Xa within target ranges. Still, pregnant women with MHV experienced both thrombosis and bleeding with anti-Xa in target range. Based on the results of this systematic review, current evidence does not support the need for anti-Xa monitoring when using LMWH as thromboprophylaxis or treatment during pregnancy. Nonetheless, the need for anti-Xa monitoring in pregnant women with MHV may require further scrutiny.

A review on the current role of platelet function testing in clinical practice follows by Mason and Rabbolini.[10] Platelet dysfunction, whether hereditary or acquired, may increase an individual's risk of spontaneous, post-traumatic, or post-operative bleeding. Conversely, increased platelet reactivity on antiplatelet agents following vascular (in particular, coronary vascular) intervention may increase the risk of thrombosis and adverse vascular events. The aim of platelet function testing is to identify and characterize platelet dysfunction in these settings, to inform bleeding/thrombosis

risk, and guide perioperative prophylactic management strategies. A vast array of screening and diagnostic tests is available for this purpose. The successful clinical application of platelet function tests depends on knowledge of their analytical strengths and limitations, as well as on correct extrapolation of derived results to a particular clinical scenario. This review critically appraises traditional and contemporary platelet function testing, focusing on their role in clinical practice.

Next is a review on the biological significance of von Willebrand Factor (VWF) O- linked glycosylation,[11] by a previous Eberhard Mammen Young Investigator Award winner, Ward[12] and colleagues. Glycosylation is a key post-translational modification, known to occur on more than half of all secreted proteins in humans. As such, the role of N- and O-linked glycan structures in modulating various aspects of protein biology is an area of much research. Given their prevalence, it is perhaps unsurprising that variations in glycan structures have been demonstrated to play critical roles in modulating protein function and have been implicated in the pathophysiology of human diseases. VWF, a plasma glycoprotein that is essential for normal hemostasis, is heavily glycosylated, containing 13 N-linked and 10 O-linked glycans. Together, these carbohydrate chains account for 20% of VWF monomeric mass, and have been shown to modulate VWF structure, function, and half-life. In this review, the authors focus on the specific role played by O-linked glycans in modulating VWF biology. Specifically, VWF O-linked glycans have been shown to modulate tertiary protein structure, susceptibility to ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) proteolysis, platelet tethering, and VWF circulatory half-life.

An original study follows from Woods et al,[13] on the differences in phenotypic parameters of types 2A and 2M von Willebrand disease (VWD) according to the affected domain by disease-causing variants (DCVs) and assessment of pathophysiological mechanisms. Types 2A and 2M VWD broadly show similar phenotypic parameters,[14] but different pathophysiological mechanisms are involved. This manuscript presents the clinical and laboratory profile of type 2A and type 2M patients genotypically diagnosed at one large center. Higher bleeding score values and larger incidence of major bleeding episodes were observed in type 2A compared with type 2M, potentially reflective of the absence of large and intermediate VWF multimers in 2A VWD. In type 2A VWD, most of DCVs appeared to be responsible for increased VWF clearance, while DCV clustered in the VWF-A1 domain resulted in more severe clinical profiles. In type 2M VWD, DCV in VWF-A1 domain showed different laboratory patterns, related to either reduced synthesis or shortened VWF survival, and DCV in VWF-A2 domain showed patterns related mainly to shortened survival. VWF-type 1 collagen binding/Ag (C1B/Ag) ratios showed different patterns according to DCV location. Specifically, C1B/Ag was much lower when DCVs were located in VWF-A2 domain in type 2A VWD, C1B/Ag with DCV in VWF-A1 domain was normal in type 2M, but with DCV in VWF-A2 domain, C1B/Ag was low. The higher frequency of major bleeding in VWD 2M patients with DCV in VWF-A2 domain than those with DCV in VWF-A1 domain could be a summative effect of abnormal C1B/Ag, on top of the reduced VWF-GPIb binding. In silico modeling suggests that DCV impairing VWF-A2 domain somehow modulates C1B to VWF-A3 domain. Concomitant normal FVIII:C/Ag and VWFpp/Ag, mainly in type 2M VWD, suggest that other nonidentified pathophysiological mechanisms, neither related to synthesis/retention nor survival of VWF, would be responsible for the presenting phenotype.

The final full-length paper in this issue of STH is another original study, by Sokou and coworkers,[15] this time a large cross-sectional study on ROTEM testing in neonates admitted to a neonatal intensive care unit. The aim of this study was to assess the coagulation profile in neonatal critical illness, and to investigate its association with disease severity and its potential prognostic role in this clinical setting. Over a period of 67 months, 423 critically ill neonates with confirmed or suspected sepsis, perinatal hypoxia, or respiratory distress syndrome, hospitalized in the authors' neonatal intensive care unit were included in the study. Demographic, clinical, and laboratory data were recorded on admission day, and arterial blood was analyzed on ROTEM analyzer using the standard extrinsically activated ROTEM assay (EXTEM). Neonatal illness severity scores (Modified NEOMOD and SNAPPE) were calculated at the same time as ROTEM analysis. Mortality during in-hospital stay was the main outcome measure. Multivariable analyses showed that a 10 mm decrease in EXTEM clot amplitude recorded at 10 minutes (A10) was significantly associated with higher mortality (odds ratio [OR] = 1.69, 95% confidence interval [CI]: 1.33–2.08). Higher modified NEOMOD (OR = 1.36, 95% CI: 1.26–1.47) and higher SNAPPE scores (OR = 1.06, 95% CI: 1.04–1.08) were also associated with increased mortality. The CT and A10 variables demonstrated the best prognostic performance among the EXTEM parameters for mortality (area under the curve [AUC] = 0.78; 95% CI: 0.69–0.86 and AUC = 0.76; 95% CI: 0.66–0.85, respectively), showing an optimal cut-off CT $\geq$63 seconds and A10 $\leq$37 mm. Using optimal cut-off values of EXTEM parameters for prediction of mortality, neonates with CT $\geq$63 seconds were 7.4 times more likely to die (OR = 7.40, 95% CI: 3.50–15.65), while neonates with A10 $\leq$37 mm were 5.8 times more likely to die (OR = 5.88, 95% CI: 2.94–12.50).

As usual for these nonthematic issues of STH, we complete the issue with some correspondence. First, Plamenova and colleagues report on the genetic background of inherited Factor XIII A-subunit deficiency in a review of the literature and description of two new cases.[16] Next, Jecko Thachil provides two letters, the first a commentary on potential clues to the pathogenesis of acquired haemophilia,[17] and the second on the terminology of the lupus anticoagulant,[18] reflecting it is possibly time to reconsider this terminology.

We once again thank all the authors to this latest issue of "Editorial Compilations" for their original and comprehensive contributions, and we hope our readership enjoys this new installment in this series.

Conflict of Interest
None declared.

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