


Preface

Editorial Compilation—XIII

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Welcome to the latest issue of *Seminars in Thrombosis and Hemostasis (STH)* published under the “banner” of “Editorial Compilation,” with this being the thirteenth such issue (► **Table 1**). Although *Seminars in Thrombosis and Hemostasis* is historically a theme-driven publication, ongoing opportunities emerge to disseminate wide-ranging contributions of current interest or controversy, which do not straightforwardly suit an ongoing themed issue. We also require a medium for enabling the publication of accepted peer-reviewed “unsolicited” manuscripts, as well as contributions from our Eberhard F. Mammen Young Investigator Award winners (see ► **Table 2** for previous Editorials related to the Eberhard F. Mammen awards). As is now standard for this compilation series, the current issue contains a mixture of articles that comprise all the above elements, as well as broadly fitting within the standard themes of “thrombosis” and “bleeding.”

This issue begins with the latest editorial related to the Eberhard F Mammen Awards, this one concerning the 2023 Most Popular Article awards for most download papers in 2022 from material published in 2021 to 2022 inclusive.¹ The second entry in this issue is fittingly a contribution from a prior (i.e., 2021) Eberhard F. Mammen Young Investigator winner,² Dr Hunter B. Moore, on the topic of fibrinolysis shutdown and hypofibrinolysis.³ Low fibrinolytic activity has been associated with pathologic thrombosis and multiple organ failure but has two separate commonly associated terms, “hypofibrinolysis” and “fibrinolysis shutdown.”

According to Dr. Moore, hypofibrinolysis is a chronic state of lack of ability to generate an appropriate fibrinolytic response when anticipated. Instead, fibrinolysis shutdown can be defined as shutdown after systemic activation of the fibrinolytic system. There has been some interchanging use of these terms to describe critically ill patients in multiple settings. The author believes that this is problematic in our understanding of the pathophysiology of disease processes related to these conditions. There is also a lack of research on the cellular mediators of these processes. The purpose of this manuscript is to review the on- and-off mechanisms of fibrinolysis in the context of low fibrinolytic states, to help define the importance of differentiating hypofibrinolysis from fibrinolysis shutdown. In many clinical scenarios, the etiology of a low fibrinolytic state cannot be determined because of ambiguity in whether a preceding fibrinolytic activation event has occurred. In this scenario, the author proposes the term low fibrinolytic activity or fibrinolysis resistance is a more appropriate descriptor, rather than using terms assumptive of hypofibrinolysis or fibrinolysis shutdown, particularly in the acute setting of infection, injury, and surgery.

This issue of STH continues with a second Young Investigator winner, Dr. Maria Selvadurai, this time part of the 2020 award “team.”⁴ Dr. Selvadurai and coauthors provide a state-of-the-art review on the mechanisms of thrombosis in heparin-induced thrombocytopenia (HIT) and vaccine-induced immune thrombotic thrombocytopenia (VITT).⁵ Both HIT and VITT are rare, iatrogenic immune-mediated

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Table 1 Past STH issues in the series “Editorial Compilation”

1. Favalaro EJ, Lippi G. Editorial Compilation I. <i>Semin Thromb Hemost.</i> 2016 Feb;42(1):5–8.
2. Favalaro EJ, Lippi G. Editorial Compilation II. <i>Semin Thromb Hemost.</i> 2016 Sep;42(6):599–602.
3. Favalaro EJ, Lippi G. Editorial Compilation III. <i>Semin Thromb Hemost.</i> 2017 Feb;43(1):4–7.
4. Favalaro EJ, Lippi G. Editorial Compilation IV. <i>Semin Thromb Hemost.</i> 2017 Sep;43(6):549–552.
5. Favalaro EJ, Lippi G. Editorial Compilation V. <i>Semin Thromb Hemost.</i> 2018 Apr;44(3):193–196.
6. Favalaro EJ, Lippi G. Editorial Compilation VI. <i>Semin Thromb Hemost.</i> 2019 Feb;45(1):5–9.
7. Favalaro EJ, Lippi G. Editorial Compilation VII. <i>Semin Thromb Hemost.</i> 2019 Jul;45(5):429–432.
8. Favalaro EJ, Lippi G. Editorial Compilation VIII. <i>Semin Thromb Hemost.</i> 2020 Jun;46(4):393–397.
9. Favalaro EJ, Lippi G. Editorial Compilation IX. <i>Semin Thromb Hemost.</i> 2021 Feb;47(1):6–10.
10. Favalaro EJ, Lippi G. Editorial Compilation X. <i>Semin Thromb Hemost.</i> 2021 Oct 47(7):754–758.
11. Favalaro EJ, Lippi G. Editorial Compilation XI. <i>Semin Thromb Hemost.</i> 2022 Mar;48(2):127–131.
12. Favalaro EJ, Pasalic L, Lippi G. Editorial Compilation XII. <i>Semin Thromb Hemost.</i> 2022 Jul;48(5):497–501.

Abbreviation: STH, Seminars in Thrombosis and Hemostasis.

conditions with high rates of thrombosis-related morbidity and mortality. HIT is a long-recognized reaction to the administration of the common parenterally administered anticoagulant heparin (or its derivatives),^{6,7} while VITT is a new, distinct syndrome occurring in response to adenovirus-based vaccines against coronavirus disease 2019 (COVID-19) and potentially other types of vaccines.^{8–10} A feature of both HIT and VITT is paradoxical thrombosis despite a characteristic low platelet count, mediated by the presence of platelet-activating antibodies to platelet factor 4. Several additional factors have also been suggested to contribute to clot formation in HIT and/or VITT, including monocyte activation, tissue factor release, prothrombotic circulating microparticles, endothelial injury, generation of neutrophil extracellular traps, complement activation, presence of procoagulant platelets, and vaccine components. In this review, the authors discuss the literature to date regarding mechanisms contributing to thrombosis in both HIT and VITT and explore the pathophysiological similarities and differences between the two conditions.

We continue the discussion of prothrombotic pathways with the next contribution, from the authorship team of Rüdiger and colleagues, who address the question of whether Vitamin D deficiency is prothrombotic.¹¹ Observational studies indicate a relationship between vitamin D deficiency and an increased risk of venous and arterial thrombotic events, but the underlying mechanisms behind this association remain uncertain. The authors provide a systematic review to explore if there is an association between decreased vitamin D levels and a prothrombotic profile. The systematic literature search initially identified 3,214 studies investigating the relationship between vitamin D and numerous hemostatic parameters. After the screening process, 18 observational and intervention studies fulfilled the criteria for being included in the systematic review. Parameters of primary hemostasis, secondary hemostasis, and fibrinolysis were investigated in six, thirteen, and fifteen of these studies, respectively. Most of the eligible studies did not identify

significant associations between decreased vitamin D levels and hemostatic parameters. Some conflicting results were found between decreased vitamin D levels and thrombin generation parameters and the tissue factor pathway inhibitor. Conflicting results were also found between decreased vitamin D levels and fibrinolytic parameters, although the evidence may point toward weak associations with some regulators of fibrinolysis, mostly decreased tissue-type plasminogen activator. Overall, this systematic review failed to identify any definitive links between vitamin D deficiency and a prothrombotic profile, and that might otherwise help explain the observed association between vitamin D deficiency and increased risk of thrombotic events. Moreover, the authors did not find any clinical evidence to confirm or refute a possible antithrombotic effect of vitamin D, concluding that larger high-quality randomized controlled trials would be needed to better elucidate the link between vitamin D deficiency and a prothrombotic risk profile.

Another systematic review from Drs. Frank and Larsen follows,¹² this time on the prognostic impact of the International Society on Thrombosis and Haemostasis (ISTH)-disseminated intravascular coagulation (DIC) score in sepsis. The ISTH diagnostic criteria for DIC are widely used for diagnosing DIC. However, the prognostic value of the score may vary between different patient populations and clinical settings. This systematic review investigates the association between ISTH DIC score and mortality in sepsis patients. The authors performed a literature search in PubMed and Embase, with inclusion criteria being studies adult and pediatric patients hospitalized with sepsis, using any sepsis definition and investigating the association between mortality and ISTH DIC score. The review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. In total, 42 studies were included. A positive association between ISTH DIC score and mortality was consistently reported, with odds ratios of death in DIC versus non-DIC patients ranging from 1.125 (95% confidence interval [CI] = 0.838–1.511) to 21.008 (95%

Table 2 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. <i>Semin Thromb Hemost</i> 2008; 34: 693–696
2. Favaloro EJ. A Tribute to Eberhard F. Mammen, M.D. (1930–2008). <i>Semin Thromb Hemost</i> 2008; 34: 703–708
3. Favaloro EJ. Welcome to the first issue of Seminars in Thrombosis and Hemostasis for 2009. <i>Semin Thromb Hemost</i> 2009; 35:1–2.
4. Favaloro EJ. Winners of the Inaugural Eberhard F. Mammen Award for Most Popular Article. <i>Semin Thromb Hemost</i> 2009; 35: 587–590
5. Favaloro EJ. Editorial. 2009 Eberhard F. Mammen Young Investigator Award Winners. <i>Semin Thromb Hemost</i> 2010; 36: 469–470
6. Favaloro EJ. Winners of the 2010 Eberhard F. Mammen Award for Most Popular Article during 2008–2009. <i>Semin Thromb Hemost</i> . 2010;36(7):685–92.
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8. Favaloro EJ. 2012 Eberhard F. Mammen award announcements. <i>Semin Thromb Hemost</i> . 2012;38:425–32.
9. Favaloro EJ. 2013 Eberhard F. Mammen award announcements. <i>Semin Thromb Hemost</i> . 39:567–74.
10. Favaloro EJ. 2014 Eberhard F. Mammen award announcements: Part I—most popular articles. <i>Semin Thromb Hemost</i> . 2014;40(4):407–12.
11. Favaloro EJ. 2014 Eberhard F. Mammen Award Announcements: Part II—Young Investigator Awards. <i>Semin Thromb Hemost</i> . 2014;40(7):718–23.
12. Favaloro EJ. 2015 Eberhard F. Mammen Award Announcements: Part I—Most Popular Articles. <i>Semin Thromb Hemost</i> . 2015;41(7):673–9.
13. Favaloro EJ. 2015 Eberhard F. Mammen Award Announcements: Part II—Young Investigator Awards. <i>Semin Thromb Hemost</i> . 2015;41(8):809–15.
14. Favaloro EJ. 2016 Eberhard F. Mammen Award Announcements: Part I—Most Popular Articles. <i>Semin Thromb Hemost</i> . 2016;42(4):325–30.
15. Favaloro EJ. 2016 Eberhard F. Mammen Award Announcements: Part II—Young Investigator Awards. <i>Semin Thromb Hemost</i> . 2017;43(3):235–241.
16. Favaloro EJ. 2017 Eberhard F. Mammen Award Announcements: Part I—Most Popular Articles. <i>Semin Thromb Hemost</i> . 2017;43(4):357–363.
17. Favaloro EJ. 2017 Eberhard F. Mammen Award Announcements: Part II—Young Investigator Awards. <i>Semin Thromb Hemost</i> . 2018;44(2):81–88.
18. Favaloro EJ. 2018 Eberhard F. Mammen Award Announcements: Part I—Most Popular Articles. <i>Semin Thromb Hemost</i> . 2018;44(3):185–192.
19. Favaloro EJ. 2018 Eberhard F. Mammen Award Announcements: Part II—Young Investigator Awards. <i>Semin Thromb Hemost</i> . 2019;45(2):123–129.
20. Favaloro EJ. 2019 Eberhard F. Mammen Award Announcements: Part I—Most Popular Articles. <i>Semin Thromb Hemost</i> . 2019;45(3):215–224.
21. Favaloro EJ. 2019 Eberhard F. Mammen Award Announcements: Part II—Young Investigator Awards. <i>Semin Thromb Hemost</i> 2020;46(2):105–113
22. Favaloro EJ. 2020 Eberhard F. Mammen Award Announcements: Part I—Most Popular Articles. <i>Semin Thromb Hemost</i> . 2020;46(4):383–392.
23. Favaloro EJ. 2020 Eberhard F. Mammen Award Announcements: Part II—Young Investigator Awards. <i>Semin Thromb Hemost</i> 2021;46(3): 229–237.
24. Favaloro EJ. 2021 Eberhard F. Mammen Award Announcements: Part I—Most Popular Articles. <i>Semin Thromb Hemost</i> . 2021 Jul;47(5):467–476.
25. Favaloro EJ. 2021 Eberhard F. Mammen Award Announcements: Part II—Young Investigator Awards. <i>Semin Thromb Hemost</i> . 2022 Apr;48(3):265–273.
26. Favaloro EJ. 2022 Eberhard F. Mammen Award Announcements: Part I—Most Popular Articles. <i>Semin Thromb Hemost</i> . 2022 Jul;48(5):502–513.

Abbreviation: STH, Seminars in Thrombosis and Hemostasis.

CI = 1.408–313.405) in adults and from 1.378 (95% CI = 1.004–1.893) to 2.99 (95% CI = 0.54–16.6) in pediatric populations, respectively. However, the DIC score only had a low-moderate positive predictive value for mortality, as

area under receiver-operator characteristics curves ranged from 0.602 (95% CI = 0.575–0.630) to 0.815 (95% CI = 0.676–0.954) in adults. Of note, only few studies adjusted for potential confounders such as age, gender, and comorbidity.

The authors conclude that the ISTH DIC score is consistently associated with sepsis-related mortality, but it is not a strong positive predictor for mortality; nevertheless, the score may still have prognostic value and its use in sepsis is encouraged.

Next is a contribution from a large team of investigators, who report on sex-related differences in platelet aggregation, from the perspective of a literature review, as supplemented with local data from a group of generally healthy individuals.¹³ The process of platelet aggregation is often influenced by several factors including sex and age. The authors performed a literature review to confirm the existence of sex-related differences in platelet aggregation. Indeed, 68 out of 78 (87%) papers found such differences; however, there remain some controversies regarding these differences, which can be due to multiple factors (age, trigger, concomitant disease, sample handling, etc.). These outcomes are discussed by the authors in conjunction with novel results obtained from a local study, in which blood samples from a total number of 53 overall healthy women and men with ages ranging from 20 to 66 years were collected. Aggregation was induced with seven different triggers (ristocetin, thrombin receptor activating peptide 6 [TRAP], arachidonic acid [AA], platelet-activating factor 16 [PAF], ADP, collagen or thromboxane A2 analog U46619) *ex vivo*. In addition, three approved antiplatelet drugs (vorapaxar, ticagrelor, or acetylsalicylic acid [ASA]) were also tested. In general, women had higher aggregation responses to some agonists (ADP and TRAP), as well as lower benefits from inhibitors (ASA and vorapaxar). The aggregatory responses to AA and TRAP decreased with age in both sexes, while responses to ADP, U-46619, and PAF were affected by age only in women. The authors conclude that more studies are needed to decipher the biological importance of sex-related differences in platelet aggregation to enable personalized antiplatelet treatment.

Another platelet-related review follows, this being from the team of Jensen et al¹⁴ and related to platelet function in acute kidney injury (AKI). Patients with AKI have increased bleeding risk, which could be partially due to acquired platelet dysfunction. The authors conducted a systematic review, and a cohort study to investigate platelet function and count in AKI and their association with AKI-related bleeding and mortality. Through a systematic literature search in PubMed and Embase, the authors identified nine studies reporting platelet function and 56 studies reporting platelet count or platelet indices in AKI patients. Overall, platelet aggregation was reduced in AKI patients in non-intensive care unit (ICU) settings but not in ICU settings, except that reduced aggregation was associated with renal replacement therapy. Thrombocytopenia in AKI was frequent and often predictive of mortality. In their cohort study, they prospectively included 54 adult ICU patients who developed AKI within 24 hours of ICU admission and 33 non-AKI ICU controls. Platelet function was measured with light transmission aggregometry and flow cytometry. AKI patients bled more frequently than non-AKI patients ($p=0.04$), and bleeding was associated with an increased 30-day mortality in AKI ($p=0.02$). However, platelet func-

tion was not different between AKI and non-AKI patients (aggregation: all $p > 0.52$; flow cytometry: all $p > 0.07$), and platelet function was not associated with bleeding in AKI. The authors conclude that reduced platelet count is frequent in AKI but that the literature on platelet function in AKI is sparse. In a cohort study, they demonstrated that patients with AKI within 24 hours of ICU admission exhibited increased bleeding tendency but this was not associated with impaired platelet function.

Another platelet-related systematic review follows, from the team of Tsallas et al, this time on pathogen reduction technologies (PRTs) and their impact on metabolic and functional properties of treated platelet concentrates.¹⁵ PRTs such as Mirasol and Intercept were developed to eliminate transfusion-transmitted infections. The impact of PRTs on platelet function during the storage period, their effect on “platelet storage lesions,” and the optimal storage duration following PRTs have not been clearly defined. The aim of this study was to systematically review the existing literature and investigate the impact of PRTs on functional alterations of PRT-treated platelets during storage. The authors identified 68 suitable studies for inclusion in their review. Despite the high heterogeneity in the literature, the results of the published studies indicated that PRTs may increase platelet metabolic activity, accelerate cell apoptosis, and enhance platelet activation, which can subsequently lead to a late exhaustion of activation potential and reduced aggregation response. However, these effects had a minor impact on platelet function during the early storage period and become more prominent beyond the fifth day of storage. The authors conclude that large *in vivo* trials are required to evaluate the effectiveness of PRT-treated platelets during storage and investigate whether their storage can be safely extended to more than 5 days, and up to the traditional 7-day storage period.

Another systematic review, this time coupled to a meta-analysis, follows, from the team of Jakobsen and colleagues, this being on mechanical heart valves, pregnancy, and bleeding.¹⁶ Anticoagulant therapy is essential in pregnant women with mechanical heart valves, to prevent valve thrombosis. The authors indicate that the risk of bleeding complications in these patients has not gained much attention. These authors, therefore, provide a systematic review and meta-analysis to investigate the prevalence of bleeding peri- and post-partum in women with mechanical heart valves, and whether bleeding risk differs across anticoagulant regimens or according to delivery mode. The study was conducted according to the PRISMA statement. Studies reporting bleeding prevalence in pregnant women with mechanical heart valves receiving anticoagulant therapy were identified through PubMed and Embase and data on bleeding complications, delivery mode, and anticoagulation therapy were extracted. A total of 37 studies were included, reporting 423 bleeding complications in 2,508 pregnancies. A meta-analysis calculated a pooled prevalence of 0.13 (95% confidence interval: 0.09–0.18) bleeding episodes per pregnancy across anticoagulant regimens. The combination of unfractionated heparin (UFH) and vitamin K antagonist (VKA) and single

VKA therapy showed the lowest risk of bleeding (8 and 12%). Unexpectedly, the highest risk of bleeding was found in women receiving a combination of low molecular weight heparin (LMWH) and VKA (33%) or monotherapy with LMWH (22%). However, this could be dose related. No difference in bleeding was found between the cesarean section versus vaginal delivery ($p = 0.08$). The authors conclude that bleeding episodes are common during pregnancy in women with mechanical heart valves receiving anticoagulant therapy and that a combination of UFH and VKA or VKA monotherapy showed the lowest risk of bleeding.

As usual for these nonthematic issues of STH, we complete this issue with some correspondence. First, Noble and colleagues¹⁷ describe findings from an observational study in their center on the frequency and clinical significance antiphosphatidyl serine (PS)/antiprothrombin (PT) antibodies in patients with antiphospholipid syndrome (APS). The authors identified a frequency of anti-PS/PT antibodies of 18%, and there was a significant association of anti-PS/PT with lupus anticoagulant (LA), IgG anticardiolipin antibodies, and specifically IgG anti-PS/PT with triple positive antiphospholipid antibodies. The authors propose that the study supports the reported potential for IgG and IgM anti-PS/PT to act as a surrogate for LA.

Lastly, there is a series of letters related to COVID-19. As previously noted, STH had been producing a series of issues entirely devoted to the topic of COVID-19, with the last such issue recently published as the inaugural issue of 2023.¹⁸ However, as the world enters a new phase of “business as usual,” these themed issues have ceased, and COVID-19-related material is now included in the regular nonthemed issue compilations. The first of these letters, from Marta et al, describe a rare case of LA-hypoprothrombinemia syndrome associated with COVID-19 and also provide a literature assessment for other reported cases.¹⁹ Their case was of a 5-year-old girl, evaluated by their hospital’s “Center for Congenital Bleeding Disorders” because of spontaneous ecchymoses on her back and thighs. All measured factors were normal, except for factor (F) II, which showed a reduced activity of 25% (reference range: 70–154%). LA was also identified by positivity in both silica clotting test and the dilute Russell’s viper venom test. Anticardiolipin and anti- β 2-glycoprotein-I IgG and IgM antibodies were in the normal range, but the anti-PS/PT assay showed a high titer of IgG (260U; reference <30U) and IgM (40U; reference <30U) antibodies. The patient was found to be positive for SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection. The patient underwent observation, and her bruising resolved spontaneously, her FII levels normalized by day 20, and the LA phenomenon completely resolved after 4 months. The authors were only able to identify one other case of COVID-19-associated LA-hypoprothrombinemia syndrome in the literature, that one being in an adult. Like most cases of LA and aPL reported to be associated with COVID-19,^{20,21} the LA in their case was transient and not characteristic of APS.

The second COVID-19-associated letter, from Wang and colleagues, is related to what some workers call “long-COVID.”²² These authors performed a study to show that

increased platelet activation could be demonstrated by elevated CD36 and P-Selectin expression in 1-year post-recovered COVID-19 patients. The authors propose that post-COVID-19 persistent platelet activation may explain why high-risk patients such as ICU patients could benefit from antiplatelet treatment regimens post-COVID-19 infection to mitigate their risk of developing thrombotic events after hospital discharge.

The final letter in this issue of STH is by Drs. Lippi and Perilli,²³ who ask the question “has ‘D-dimeritis’ worsened during the COVID-19 pandemic”? COVID-19 represents a prothrombotic disorder, and thus an associated increased risk of developing acute thrombotic events, both venous and arterial. Therefore, D-dimer values are very frequently elevated in patients with acute SARS-CoV-2 infection, correlate with the clinical phenotype, and predict the risk of developing thrombosis and multiple organ failure.²⁴ It is consequently not surprising that the number of D-dimer test requests may have undergone a paramount increase throughout the COVID-19 pandemic, since this biomarker provides a valuable, almost unreplaceable contribution to the diagnostic approach, clinical decision-making, risk stratification, and managed care of patients with COVID-19. The authors undertook a PubMed search to identify a huge surge in D-dimer-related publications over the years 2020 to 2022, most of which appeared to be related to COVID-19. Moreover, they investigated D-dimer test counts at their institution to show increases of 5.5-fold and 3.1-fold in 2021 and 2022 respectively, compared with 2019 numbers. Remarkably, in some departments, the increases were 34.5- and 13.8-fold in 2021 and 2022, respectively, for the pulmonology and infectious diseases units, and 23.1- and 12.9-fold in 2021 and 2022, respectively, for ICUs. Such increases can be compared with another recent report from Australia, which showed general increases in D-dimer testing of up to nine-fold in a series of hospital-associated laboratories and according to a timeline of COVID-19 “waves,” with similar increases across all metropolitan hospital sites, where the burden of COVID-19 patients would be highest, as compared with rural/regional sites.²⁵

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

Conflict of Interest

None declared.

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