Preface

Editorial Compilation XII

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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 twelfth 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, and which do not straightforwardly suit an ongoing themed issue. We also require a medium for enabling publication of accepted peer reviewed "unsolicited" manuscripts, as well as additional contributions from our Eberhard F. Mammen Young Investigator Award winners (►**Table 2**). As it is now standard for this compilation series, the current issue contains a mixture of articles that comprises 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 Eberhard F Mammen Awards, this one related to the 2022 Most Popular Article awards for most downloaded papers from 2020 to 2021 inclusive.[1] The second entry in this issue is fittingly a contribution from a prior (2020) Young Investigator winner,[2] Hanny Al-Samkari, on the topic of hereditary hemorrhagic telangiectasia (HHT),[3] the second most common hereditary bleeding disorder in the world. Management of bleeding in HHT is currently undergoing a paradigm shift. Disease-modifying antiangiogenic therapies capable of achieving durable hemostasis via inducing telangiectasia regression have emerged as a highly-effective and safe modality to treat epistaxis and gastrointestinal bleeding in HHT. While evidence to date is incomplete and additional studies are ongoing, patients presently in need are being treated with antiangiogenic agents off-label. Intravenous bevacizumab, oral pazopanib, and oral thalidomide are the three targeted primary angiogenesis inhibitors, with multiple studies describing both reassuring safety and impressive effectiveness in the treatment of moderate-to-severe HHT-associated bleeding. However, there is a paucity of guidance in the literature at present, including the published HHT guidelines, addressing the practical aspects of antiangiogenic therapy for HHT in clinical practice. This review article and practical evidence-based guide aim to fill this unaddressed need, synthesizing published data on the use of antiangiogenic agents in HHT, relevant data for their use outside of HHT, and expert guidance where evidence is lacking. After a brief review of principles of bleeding therapy in HHT, guidance on hematologic support with iron and blood products, and alternatives to antiangiogenic therapy, this article examines each of the aforementioned antiangiogenic agents in detail, including patient selection, initiation, monitoring, toxicity management, and discontinuation. With proper, educated use of antiangiogenic therapies in HHT, patients with even the most severe bleeding manifestations can achieve durable hemostasis with minimal side effects, thus dramatically improving health-related quality of life and potentially altering the disease course.

This issue of STH continues with the theme of bleeding, with a review from Samii et al on gastrointestinal bleeding in congenital bleeding disorders.[4] Gastrointestinal bleeding is a serious, intractable, and potentially life-threatening condition. There is considerable heterogeneity in gastrointestinal bleeding phenotypes among congenital bleeding disorders, making gastrointestinal bleeding difficult to manage. Although gastrointestinal hemorrhages are rarely encountered in congenital bleeding disorders, their severity in some patients makes the need for a comprehensive and precise assessment of underlying factors and management approaches imperative. Initial evaluation of gastrointestinal bleeding begins with assessment of hematological status; gastrointestinal bleeding should be ruled out in patients with chronic anemia, and in presentations that include

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Table 1 Past STH issues in the series "Editorial Compilation"

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

hematemesis, hematochezia, or melena. High-risk patients with recurrent gastrointestinal bleeding require urgent interventions such as replacement therapy for treatment of coagulation factor deficiency. However, the best management strategy for coagulation factor deficiency-related bleeding remains controversial. While several investigations have identified congenital bleeding disorders as potential risk factors for gastrointestinal bleeding, research has focused on assessing the risks for individual factor deficiencies and other congenital bleeding disorders. This review highlights recent findings on prevalence, management strategies, and alternative therapies of gastrointestinal bleeding related to coagulation factor deficiencies, and platelet disorders.

A few contributions related to platelets follow. First is a systematic review on flow cytometric assessment of changes in platelet reactivity after acute coronary syndrome (ACS) by Pedersen et al.[5] Increased platelet activity is an important predictor for recurrent cardiovascular events in patients with ACS. Flow cytometry is an advanced method for the evaluation of platelet activity. The authors aimed to summarize the current literature on dynamic changes in platelet activity analyzed by flow cytometry in patients with ACS. Employing the guidelines of Preferred Report Items for Systematic Reviews and Meta-Analyses (PRISMA), they searched PubMed and Embase to identify studies assessing platelet activity with flow cytometry in ACS patients in the acute phase (baseline) and at follow-up in a more stable phase. In the 12 included studies, fibrinogen receptor, α-granule secretion, platelet reactivity index, monocyte-platelet aggregates, neutrophil-platelet aggregates, and reticulated platelets were analyzed. The fibrinogen receptor and α-granule secretion were either unchanged or lower during follow-up measurements than in the acute phase. Platelet reactivity index showed inconsistent results. Values of monocyte-platelet aggregates and neutrophil-platelet aggregates were lower at follow-up than at baseline. Reticulated platelets were either unchanged or lower at 1 to 2 months follow-up, and also lower at 5 months to 1-year follow-up compared with baseline. Overall, flow cytometric analyses of platelet function in ACS patients showed that platelet activity was lower at follow-up than at baseline. However, in some patients, platelet activity remained unchanged from baseline to follow-up, possibly indicating a sustained high platelet activity that may increase the risk of recurrent cardiovascular events.

Another systematic review on platelets follows, this time on the drug colchicine as a modulator of platelet function, by Reddel et al.[6] Colchicine is a microtubule inhibitor and anti-inflammatory agent used to treat a range of conditions involving inflammasome activation in monocytes and neutrophils, and it is now known to prevent coronary and cerebrovascular events. In vitro studies dating back more than 50 years showed a direct effect of colchicine on platelets, but as little contemporary attention has been paid to this area, the authors have critically reviewed the effects of colchicine on diverse aspects of platelet biology in vitro and in vivo. The authors searched Embase, Medline, and PubMed for articles testing platelets after incubation with colchicine and/or reporting a clinical effect of colchicine treatment on platelet function. They identified 98 relevant articles and grouped their findings based on the type of study and platelet function test. In vitro colchicine inhibits traditional platelet functions, including aggregation, clotting, degranulation, and platelet-derived extracellular vesicle formation, although many of these effects were reported at apparently supraphysiological concentrations. Physiological concentrations of colchicine inhibit collagen- and calcium ionophore-induced platelet aggregation and internal signaling. There have been limited studies of in vivo effects on platelets. The colchicine–platelet interaction has the potential to contribute to colchicine-mediated reduction in cardiovascular events, but there is a pressing need for high-quality clinical research in this area.

Next, is another systematic review, this one on tranexamic acid and its potential anti-inflammatory effects by Okholm et al.[7] Tranexamic acid is an antifibrinolytic drug primarily used for reducing blood loss in patients with major bleedings. Animal and cell studies have shown that tranexamic acid might modulate the inflammatory response by either enhancing or inhibiting cytokine levels. Furthermore,

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. Semin Thromb Hemost 2008;34:693–696
2. Favaloro EJ. A tribute to Eberhard F. Mammen, M.D. (1930–2008). Semin Thromb Hemost 2008;34:703–708
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):685–92
7. Favaloro EJ. 2011 Eberhard F. Mammen Award announcements. Semin Thromb Hemost 2011;37(5):431–9
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9. Favaloro EJ. 2013 Eberhard F. Mammen Award announcements. Semin Thromb Hemost 39:567–74
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11. Favaloro EJ. 2014 Eberhard F. Mammen Award Announcements: part II - Young Investigator Awards. Semin Thromb Hemost 2014;40(7):718–23
12. Favaloro EJ. 2015 Eberhard F. Mammen Award announcements: part I-most popular articles. Semin Thromb Hemost 2015;41(7):673–9
13. Favaloro EJ. 2015 Eberhard F. Mammen Award announcements: part II-Young Investigator Awards. Semin Thromb Hemost 2015;41(8):809–15
14. Favaloro EJ. 2016 Eberhard F. Mammen Award announcements: part I - most popular articles. Semin Thromb Hemost 2016;42(4):325–30
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;46(3): 229–237
24. Favaloro EJ. 2021 Eberhard F. Mammen Award announcements: part I-most popular articles. Semin Thromb Hemost 2021 Jul;47(5):467–476
25. Favaloro EJ. 2021 Eberhard F. Mammen Award announcements: part II-Young Investigator Awards. Semin Thromb Hemost 2022 Apr;48(3):265–273

recent human studies have found altered inflammatory biomarkers in patients receiving tranexamic acid, compared with patients who did not. In this systematic review, the authors investigated the effect of tranexamic acid on inflammatory biomarkers in different patient groups. A systematic literature search was conducted on the databases PubMed and Embase to identify all original articles that investigated inflammatory biomarkers in patients receiving tranexamic acid and compared them to a relevant control group. The review was performed according to the PRISMA guidelines, and the literature search was performed in late 2021. Thirty-three studies were included, among which 14 studies

compared patients receiving tranexamic acid with patients getting no medication, another 14 studies investigated different dosing regimens of tranexamic acid, and finally five studies examined the administration form of tranexamic acid. The review also suggests that tranexamic acid has an anti-inflammatory effect in patients undergoing orthopaedic surgery illustrated by decreased levels of C-reactive protein and interleukin-6 in patients receiving tranexamic acid compared with those receiving no or lower doses of tranexamic acid. However, the anti-inflammatory effect was not found in patients undergoing cardiac surgery, pediatric craniosynostosis patients, or in rheumatoid arthritis patients. The inflammatory response was not affected by the administration form of tranexamic acid (oral, intravenous, or topical). In conclusion, an anti-inflammatory effect of tranexamic acid was consistently found among orthopaedic patients only.

Another inflammation-related review follows, this one on the effects of inflammation on hemostasis in acutely ill patients with liver disease, by another 2020 Young Investigator Award Winner, Ellen G. Driever and Ton Lisman.[8] Patients with liver diseases are in a rebalanced state of hemostasis, due to simultaneous decline in pro- and anticoagulant factors. This balance seems to remain even in the sickest patients, but it is less stable and might destabilize when patients develop disease complications. Patients with acute decompensation of cirrhosis, acute-on-chronic liver failure, or acute liver failure often develop complications associated with changes in the hemostatic system, such as systemic inflammation. Systemic inflammation causes hemostatic alterations by adhesion and aggregation of platelets, release of von Willebrand factor (VWF), enhanced expression of tissue factor, inhibition of natural anticoagulant pathways, and inhibition of fibrinolysis. Laboratory tests of hemostasis in acutely-ill liver patients may indicate a hypocoagulable state (decreased platelet count, prolongations in prothrombin time and activated partial thromboplastin time, decreased fibrinogen levels) due to decreased synthetic liver capacity or consumption, or a hypercoagulable state (increased VWF levels, hypofibrinolysis in global tests). Whether these changes are clinically relevant and should be corrected with antithrombotic drugs or blood products is incompletely understood. Inflammation and activation of coagulation may cause local ischemia, progression of liver disease, and multiorgan failure. Anti-inflammatory treatment in acutely ill liver patients may be of potential interest to prevent thrombotic or bleeding complications and halt progression of liver disease.

Another systematic review on the role of plasminogen activator inhibitor type 1 (PAI-1) in placenta-mediated pregnancy complications follows by Agersnap et al.[9] PAI-1 is the main inhibitor of fibrinolysis. The *PAI-1* gene (*SERPINE1*) harbors genetic variants with the potential of modifying plasma levels of PAI-1. A delicate balance exists between the coagulation and fibrinolytic system, and changes in PAI-1 have been suggested to compromise establishment of a successful pregnancy. Therefore, this systematic review investigated the association between genetic variants and/or plasma levels of PAI-1 and placenta-mediated pregnancy complications. An extensive literature search was conducted in PubMed, Embase, and Web of Science in mid-2021. All studies underwent quality rating according to The Study Quality Assessment Tools checklist provided by National Heart, Lung and Blood Institute. A total of 71 studies were included, among which 60 studies investigated *PAI-1* genotypes and 11 studies measured PAI-1 plasma levels. In 32 out of 59 studies, no association was found between the *PAI-1* 4G/5G polymorphism (rs1799768) and placenta-mediated pregnancy complications, which was stated as no significant difference in the genotype distribution comparing women with and without placenta-mediated pregnancy complications or no significantly increased odds of placenta-mediated pregnancy complications carrying the 4G/4G or 4G/5G genotype. Eight out of 11 studies reported significantly higher PAI-1 plasma levels in preeclamptic women than in women without preeclampsia. In conclusion, no clear evidence indicates that *PAI-1* polymorphisms are associated with placenta-mediated pregnancy complications, and the possible association between high PAI-1 plasma levels and preeclampsia needs further investigations. Thus, investigation of *PAI-1* genotypes and PAI-1 plasma levels does not currently seem to have a place in daily clinical practice managing placenta-mediated pregnancy complications

As usual for these nonthematic issues of STH, we complete the issue with some correspondence. First, Daşdemir and Kaya[10] provide a commentary on an earlier publication in this journal related to cancers in patients with von Willebrand disease (VWD),[11] also describing a case of a parathyroid adenoma in a young girl with type 3 VWD. Franchini et al, the lead author of the prior publication,[11] provides a reply.[12] Lastly, Arachchillage et al provide some useful snippets on the management of lupus anticoagulant positive patients on cardiopulmonary bypass.[13]

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 latest instalment in this series.

Conflict of Interest
None declared.

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