Welcome to the latest issue of *Seminars in Thrombosis and Hemostasis* (STH) published under the “banner” of “Editorial Compilation,” with this being the fifth such issue. Although STH is primarily a theme driven publication, the opportunity intermittently arises to publish issues containing more wide-ranging chapters of current interest and controversy, which do not quite match a current themed issue in progress. We also require a medium to enable publication of contributions from our Eberhard F. Mammen Young Investigator Award (YIA) winners.1–7 As now standard for this compilation series, the current issue has a mixture of content that comprises all these elements, broadly fitting within the separate themes of “thrombosis” and “bleeding.”

This issue begins with the contributions from two of our most recent (2016 and 2017) Eberhard F Mammen YIA winners.6,7 The first, representing the contribution from YIA winner Ivar van Asten,8 discusses the coming of age of flow cytometry for platelet function diagnostics. Laboratory testing of (inherited) platelet function disorders mainly comprises aggregation and secretion assays. These may be suitable for diagnosing specific, typically severe, platelet function disorders but perhaps are not reliable enough for diagnosing mild platelet function disorders, as well as having difficulty when assessing disorders associated with low platelet count. Flow cytometric assessment of platelet reactivity will expectedly provide additional value during such diagnostic work-ups because the process only requires a small volume of whole blood and allows measurements of platelet function in thrombocytopenic samples. Flow cytometry is often used to evaluate platelet function in the research setting, but such assays will require clinical validation before effective use as routine diagnostic tools. The lack of any gold standard test for mild platelet function disorders is the main challenge in the validation of innovative platelet function diagnostic tests. This review aims to address the many applications of flow cytometry in the diagnostic work-up of platelet function testing and discusses the challenges in introducing new tools for diagnosing platelet function disorders.

Next is the contribution from YIA winner Jasmine Tay,9 who discuss the small noncoding ribonucleic acids (RNAs) called microRNAs (or miRNAs), which have been implicated in a myriad of diseases. Accumulating evidence also indicates their potential high value as diagnostic and prognostic biomarkers. Although their roles in hemostasis and coagulation pathways are less defined, many studies have demonstrated their participation in regulating key factors of hemostasis. However, the mounting challenges associated with the accurate measurement of circulating miRNAs and the involvement of platelet activation in contributing to the circulating miRNA expression profile introduce further complexity to the study of thrombosis-associated miRNAs. This review outlines the current knowledge of miRNAs that have been postulated to regulate key hemostatic factors, and miRNA diagnostic panels in thrombotic disease, with a focus on experimental fundamentals, such as selecting conditionspecific reference controls, considerations that are crucial for accurate evaluation of miRNAs in the context of disease biomarkers.

Continuing the discussion around miRNAs, this time in relation to their evolving role in endothelial cell dysfunction in response to infection, is the review from Watkin et al.10 These authors reflect that miRNAs are short noncoding RNA molecules responsible for translational repression and silencing of target genes through binding to the messenger RNA, are found in all eukaryotic cells, and play a critical role in virtually all physiological processes, including those within the cardiovascular system, where they influence cellular development, differentiation, cardiovascular function, hemostasis, and programmed cell death. Dysregulated miRNA expression is associated with several conditions, ranging from cancer and
autoimmune disease to infection. Progressively, it has become increasingly clear that miRNAs are important components of the host response to microbes. The cardiovascular system, coupled with cells of the innate immune system, provide the initial interaction and first response to microbial infection, respectively. This review presents the current state of knowledge regarding the role of miRNAs, with emphasis on their role in controlling endothelial cell function.

Kell and Pretorius then discuss sepsis, septic shock, systemic inflammatory response syndrome (SIRS), and multiple organ dysfunction syndrome (MODS), and the possible role of prion/amyloid forms of fibrin in the process. The authors assert that a well-established development of increasing disease severity leads to sepsis through SIRS, septic shock, MODS, and cellular and organismal death. Less commonly discussed, however, are the equally well-established coagulopathies that accompany this. The authors argue that a lipopolysaccharide-initiated (often disseminated intravascular) coagulation is accompanied by a proteolysis of fibrinogen such that formed fibrin is both inflammatory and resistant to fibrinolysis. Furthermore, the form of fibrin generated is amyloidogenic in nature because much of its normal α-helical content is transformed to β-sheets, as occurs with other proteins in established amyloidogenic and prion diseases. The authors hypothesize that these processes of amyloidogenic clotting and the attendant coagulopathies play a role in the passage along the above pathways to organismal death and that their inhibition would be of significant therapeutic value, a claim for which they believe is considerable emerging evidence.

The guest editors of this issue of Seminars in Thrombosis and Hemostasis, Lippi and Favaloro, then discuss venous and arterial thrombosis, asking the question: are these two sides of the same coin? Both arterial and venous thromboses are sustained by development of the intraluminal thrombosis; however, these are respectively within the venous and arterial systems. The composition and structure of arterial and venous thrombi have been historically considered as being very different: arterial thrombi (conventionally defined as “white”) have been traditionally proposed to be composed mainly of fibrin and platelet aggregates, whereas venous thrombi (conventionally defined as “red”) have been proposed as mostly being enriched in fibrin and erythrocytes. This archaic dichotomy seems increasingly questionable since it barely reflects the in vivo pathophysiology of thrombus formation. Both types of thrombi are actually composed of a complex fibrin network but importantly also contain essentially the same blood-borne cells (i.e., red blood cells, leukocytes, and platelets). The authors argue that it is only the relative content of these individual elements that differ between venous and arterial clots or, otherwise, between thrombi generated under different conditions of blood flow and shear stress. Convincing evidence also suggests that either white or red intracoronary thrombi may be present in patients with myocardial infarction, and, even more importantly, red thrombi may be more prone to distal embolization during percutaneous coronary intervention than those with a lower content of erythrocytes. Conversely, it is also now accepted that components traditionally considered to be involved “only” in arterial thrombosis are also represented in venous thrombosis. Thus, platelets comprise important components of venous clots, although they may be present in lower amounts here than in arterial thrombi, and von Willebrand factor (VWF) is also represented in both arterial and venous thrombi. Importantly, such evidence also supports the concept that adjunctive treatment normally associated with the prevention of arterial thrombosis (e.g., aspirin) may have a role in the prevention and treatment of venous thrombosis.

Continuing the discussion of thrombosis, and in a similar juxtaposition, Calabro et al discuss venous thromboembolism (VTE), this time specifically regarding the potential role of VWF in the pathogenesis. VWF is normally discussed within the field of bleeding, being deficient or defective in von Willebrand disease (VWD). Considered the most common inherited bleeding disorder. Being a major determinant of hemostasis and clot formation, in both arteries and veins, if considered within the process of thrombosis, VWF is mainly known for its role in arterial thrombosis. However, several studies now suggest a pathogenic role of VWF and its regulator ADAMTS13 in VTE. VTE, in turn, is a frequent cause of disability and mortality worldwide, and nongenetic and genetic factors, including gene mutations and polymorphisms, aging, hormone status, ABO blood groups, and systemic inflammation, have been involved in the modulation of both VTE predisposition and plasma levels of VWF. In several clinical settings, including inflammatory disease and cancer, VWF and ADAMTS13 are currently being investigated as possible determinants of vein thrombosis. These data also indicate VWF as a potential therapeutic target in the management of VTE. Several studies report unselective antagonism of VWF for drugs used in daily clinical practice, including heparin and statins. Selective inhibition of VWF pathway has recently been tested in animal models of arterial and venous thromboses as a novel therapeutic strategy to prevent platelet aggregation and thrombosis, to promote vein lumen recanalization, and to improve vein valve competency with excellent safety profile. In this review, the authors summarize the role of VWF in VTE, focusing on clinical and potential therapeutic implications.

One more contribution related to thrombosis, this time its management, is then provided by Lim et al. The advent of direct oral anticoagulants (DOACs) has revolutionized anticoagulation management in both stroke prevention and VTE treatment/prevention. Clinical trials and secondary real-world data have shown that DOACs have similar efficacy and, in some cases, improved bleeding safety profiles compared with vitamin K antagonists. Together with benefits of patient convenience, this has shifted the risk–benefit ratio toward long-term anticoagulation. However, current VTE risk assessment models are based on vitamin K antagonists and do not take into account the new paradigm of DOACs. Therefore, challenges to the thrombosis community remain to determine patients who would benefit from long-term anticoagulation in the DOAC era. The authors therefore review the current literature on risks and benefits of DOACs and their potential role in long-
term VTE thromboprophylaxis as well as in current risk assessment models. The increasing use of DOACs, led by their convenience of use and generally lower bleeding rates, calls for a reevaluation of the current models as the benefits of long-term anticoagulation may begin to outweigh risks and inconvenience associated with their predecessors.

Turning to bleeding and hemorrhage, Alavi et al then comprehensively cover the topic of intracranial hemorrhage (ICH) in the light of congenital factor XIII deficiency (FXIIID). ICH is a medical emergency. In congenital bleeding disorders, ICH is a devastating presentation accompanied with a high rate of morbidity and mortality. Prevalence of ICH is highly variable among congenital bleeding disorders, but the highest incidence (30%) is observed in FXIIID. ICH is less common in afibrinogenemia and FVIII, FIX, severe FVII, and FX deficiencies, and is rare in severe FV and FII deficiencies, type 3 VWD, and inherited platelet function disorders. In FXIIID, this diathesis most often occurs after trauma in children, whereas spontaneous ICH is more frequent in adults. Approximately 15% of patients with FXIIID and ICH die, and bleeding causes 80% of deaths in this coagulopathy. Although the bleed most commonly is intraparenchymal (>90%) in FXIIID, epidural, subdural, and subarachnoid hemorrhages have also been reported, albeit rarely. As ICH causes neurologic complications, early diagnosis can prevent further expansion of the hematoma and secondary damage. Neuroimaging plays a crucial role in the diagnosis of ICH, but signs and symptoms in patients with severe FXIIID should trigger replacement therapy even before the diagnosis is established. While a high dose of FXIII concentrate can reduce the rate of morbidity and mortality of ICH in FXIIID, it may occasionally trigger inhibitor development, thus complicating ICH management and future prophylaxis. Nevertheless, replacement therapy is the mainstay of treatment for ICH in FXIIID. Neurosurgery is performed in patients with FXIIID and epidural hematoma, and a hemorrhage diameter exceeding 2 cm or volume of ICH greater than 30 cm³. Contact sports are not recommended in people with FXIIID, as these can elicit ICH. However, a considerable number of safe sports and activities have been suggested to have more benefits than dangers for patients with congenital bleeding disorders and are hence considered suitable for these patients.

Discussion around ICH is continued by Arachchilage et al, this time as associated with extracorporeal membrane oxygenation (ECMO) for severe respiratory failure. These authors describe ICH as a serious complication in patients receiving veno-venous ECMO (VV-ECMO) as well as being associated with high mortality. However, it is unknown whether ICH may be a consequence of the ECMO or of an underlying disease. The authors therefore performed a study aiming to assess the incidence of ICH at initiation and during the course of VV-ECMO and its associated mortality. A second aim was to identify clinical and laboratory measures that could predict the development of ICH in severe respiratory failure. Data were collected from a total number of 165 patients receiving VV-ECMO in a single tertiary center and treated according to a single protocol. Only patients who had a brain computed tomography (CT) within 24 hours of initiation of ECMO (n = 149) were included for analysis. The prevalence and incidence of ICH at initiation and during the course of VV-ECMO (median 9 days) were 10.7% (16/149) and 5.2% (7/133), respectively. Thrombocytopenia and reduced creatinine clearance (CrCl) were found to be independently associated with increased risk of ICH on admission; odds ratio (95% confidence interval [CI]): 22.6 (2.6–99.5) and 10.8 (5.6–16.2). Thirty-day (but not 180-day) mortality was significantly higher in patients with ICH on admission versus those without (37.5% [6/16] vs. 16.4% [22/133]), p = 0.03; and 43.7% [7/16] vs. 26.3% [35/133]); p = 0.15, respectively). The authors thus conclude that reduced CrCl and thrombocytopenia are associated with ICH at initiation of VV-ECMO. The higher incidence of ICH at initiation suggests that it is more closely related to the severity of the underlying lung injury than to the VV-ECMO itself. ICH at VV-ECMO initiation was also associated with early mortality.

Finally, Botero et al report another original study, this one reporting on factor IX gene (F9) genotyping in hemophilia B (HB), as used for molecular confirmation of affected individuals, for carrier testing, facilitating the identification of those at risk for anaphylaxis/inhibitors (associated with large deletions), and assisting in assigning disease severity. Due to test costs, optimal test use involves pre-/posttest counseling, and appropriate patient and test selection (e.g., mutation screening [F9MS] vs. known mutation [F9KM] testing). The authors’ article aims to review the trends and outcomes of F9 genotyping orders and describe the spectrum of variants identified in a sample of individuals in their reference laboratory (Mayo Clinic Special Coagulation DNA Diagnostic Laboratory). The authors performed a retrospective review of recent consecutive orders submitted to them, for a total of 133 orders (38%) identified for men: 118 (88%) were F9MS and 15 (12%) F9KM. Interestingly, 209 orders were identified for women: 178 (85%) were F9MS and 31 (15%) F9KM, where 30% of tests yielded negative results. Overall, 17 previously unreported variants were identified. The authors conclude that although F9 genotyping may provide useful information for HB management, 18% of orders received were inappropriate (and thus not progressed), and almost half of all orders were received without relevant clinical information, thus reaffirming the need for ongoing scrutiny of submitted orders. Optimal patient and test selection is important, as is the accurate interpretation of variants identified. Most of the pathogenic variants identified were point mutations, with very few large deletions, consistent with the literature.

As typical for this series, several correspondences are also included in this issue. First, Alsermani et al report an interesting case of hematidrosis and then further discuss this fascinating phenomenon in light of the literature, as also further discussed in an accompanying commentary by the guest editors to the issue. Then, Tufano et al discuss two cases of cytomegalovirus-associated splanchic vein thrombosis in immunocompetent patients, as well as a review of the literature. Finally, Mattioli et al discuss issues related to heparin-induced thrombocytopenia in the setting of cardiac surgery patients.
As always, we would like to thank all the authors in this latest issue of “Editorial Compilations” for their original and comprehensive contributions. We also hope that you, representing the readership of this journal, find this issue of substantial interest. This will, of course, be determined in time, as measured and established for previous issues of this journal.

References
15. Li HY, Nandurkar H, Ho P. Direct oral anticoagulants (DOACs) and the paradigm shift in management of venous thromboembolism. Semin Thromb Hemost 2018;44(03):261–266