Editorial

Reflections on World Thrombosis Day 2024

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Thromb Haemost

On the occasion of World Thrombosis Day, our four journals: *Thrombosis and Haemostasis*, *TH Open*, *Seminars in Thrombosis and Hemostasis* as well as *Hämostaseologie—Progress in Haemostasis* join forces in a collaborative editorial to share and emphasize our commitment to advancing research, education, and clinical practice, and reducing the impact of thrombosis worldwide, as an entity that gives rise and contributes to a major part of the morbidity and mortality from cardiovascular diseases and beyond.

We highlight here recent publications from our journals, which we hope will have an impact on understanding and management of thrombosis.

Exploring Thromboinflammation and Platelet Signaling in the Evolving Landscape of Thrombosis

Initially focused on the classical pathways of clot formation, thrombosis research now explores how inflammation and intricate platelet signaling contribute to thrombotic events, offering a more comprehensive view of thrombosis and its underlying processes.

Thrombus formation is closely linked to the innate immune response, driving leukocyte recruitment, neutrophil extracellular trap formation, and complement activation. These immune processes amplify thrombosis by activating platelets, now recognized as key players in immunity, and promoting fibrin formation. The comprehensive review by Sachetto and Mackman[1] explored the influence of tissue factor expression in monocytes and its induction by lipopolysaccharide across various diseases. This publication, which mostly covered sepsis and venous thrombosis, provided valuable insights into these pathological conditions.

The coronavirus disease 2019 (COVID-19) pandemic also recently highlighted the significant role of thromboinflammation, and antiplatelet strategies have naturally been proposed for managing thrombotic complications associated with COVID-19. In this context, Rolling et al[2] assessed the effects of P2Y12 inhibition in COVID-19 and, consistent with prior research on atherosclerosis, observed the formation of increased monocyte–platelet aggregate formation upon SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection. Their findings also showed that P2Y12 inhibition effectively suppressed these aggregates in COVID-19 patients. A study by Zou and colleagues[3] explored the signaling pathways that govern reversible versus irreversible integrin activation, offering new insights into the molecular mechanisms regulating the transience of integrin activation, potentially guiding the optimization of effective antiplatelet therapies. Platelets also express immune-like receptors such as C-type lectin-like receptor 2 (CLEC-2), which has emerged as a potential therapeutic target in addressing thromboinflammation. This was challenged by the study from Bourne et al,[4] as they demonstrated that CLEC-2, although crucial for thrombus growth in mice, appeared to be dispensable for human platelet thrombus formation under arterial shear. Such research is crucial in the quest for novel therapeutic targets and the development of new antithrombotic drugs, which may or may not prove applicable in clinical settings.

Chronic inflammatory conditions have also been associated with higher risk of venous thromboembolism (VTE). Boccatonda and colleagues[5] explored the connection between gastrointestinal chronic inflammation in inflammatory bowel disease (IBD) and VTE, its pathophysiology, and

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DOI https://doi.org/10.1055/s-0044-1791650.
ISSN 0340-6245.

available treatment options. They highlighted the inflammation-induced hypercoagulable state as the primary mechanism for VTE in IBD, and its exacerbation by endothelial dysregulation as well as key factors including coagulation system activation, platelet abnormalities, and fibrinolysis disruption, with gut microbiome dysregulation playing a pivotal role in amplifying systemic inflammation.

Transitioning from understanding the fundamental mechanisms of thromboinflammation, our focus now shifts towards studies aiming to improve clinical management of thrombosis.

A Tailored Approach for Thrombosis Management

Tailoring anticoagulation strategies to meet individual patient needs continues to be one of our most important foci to balance the risk of thrombosis and bleeding with thromboprophylaxis. Here we will highlight studies that addressed management and effectiveness of anticoagulation therapy in the context of various factors, including disease complexity, polypharmacy, perioperative procedures, age, genetics, and pregnancy. Considering these factors in each specific clinical context is essential for a comprehensive and integrated approach.

In their report from the GLORIA-AF Registry, Romiti et al[6] put forward the complexity of clinical management and higher risk of adverse outcomes of patients with atrial fibrillation (AF). The authors identified suboptimal oral anticoagulation prescribing and increased discontinuations and called for additional efforts, including an integrated care approach, to improve the management and prognosis of these patients. In the context of AF, the Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4) demonstrated that early rhythm control significantly reduced the risk of death from cardiovascular causes, stroke, and hospitalization. However, the trial's "one-size-fits-all" approach to early rhythm control raises questions about its applicability in clinical practice. A nationwide cohort study by Chao et al[7] supported the trial's findings, showing that in routine daily care, early rhythm control was linked to lower risks of ischemic stroke, heart failure, mortality, and composite adverse events compared to standard care.

Polypharmacy, commonly defined as the simultaneous use of five or more medications, is especially relevant in elderly patients with AF who often have multiple comorbidities, experience falls, and suffer from frailty or dementia. Grymonprez et al[8] confirmed that polypharmacy was linked to poorer outcomes, including higher risks of bleeding and mortality and called for the use of direct oral anticoagulants (DOACs) in patients with polypharmacy.

In an opinion piece, Tafur et al[9] proposed an anticoagulation stewardship model to tackle the challenges of the commonly encountered clinical issue of perioperative anticoagulation management. The authors used a case-based approach along with implementation of science to improve standardized, evidence-based care, which could solve many issues associated with periprocedural management of anticoagulation.

Just as the elderly population faces unique challenges in thrombosis management, pediatric health encounters distinct issues in this area. Incidence of VTE in children has risen significantly over the past two decades, largely due to advancements in medical techniques and increased survival rates of children with chronic conditions. In their review, Spiezia and colleagues[10] outlined the rationale for rivaroxaban oral suspension in clinical practice, referring to the EINSTEIN JUNIOR randomized trial and, detailing its various indications and benefits across different types of pediatric VTEs. Glonnegger and colleagues[11] evaluated the clinical outcomes of magnetic resonance imaging follow-up and early anticoagulation in pediatric cerebral venous sinus thrombosis (CVST) patients treated with heparin. Remarkable recanalization in all patients highlighted the importance of conducting further research to refine and optimize anticoagulant therapy for pediatric CVST. Lemierre syndrome is another potentially life-threatening condition affecting healthy young adults and adolescents, which is primarily marked by neck vein thrombosis and septic embolism following bacterial infection. Pleming et al[12] highlighted that arterial involvement did occur in one-10th of patients and was associated with higher risks of all-cause death and long-term clinical sequelae, emphasizing the need for increased vigilance in identifying and managing these complications.

While age should call for differentiated thrombosis management, genetics also can influence how patients respond to anticoagulants. The challenge associated with anticoagulation in East Asian patients for whom bleeding risk is higher compared to Western populations was emphasized by a timely publication of an expert consensus paper from Europe and the Asia-Pacific on bleeding risk assessment.[13] The updated guidelines from the Asia-Pacific Heart Rhythm Society on stroke prevention in AF reaffirmed the significance of the Atrial fibrillation Better Care pathway and highlighted the recommendation to prioritize DOACs over vitamin K antagonists. Another setting in which anticoagulation management must be assessed carefully is pregnancy.

The Italian Position Paper by Campello et al[14] on the management of pregnant women with mechanical heart valves provided clinically important guidance on anticoagulation strategies in this specific clinical setting. The authors emphasized that no single anticoagulation approach was universally safe for both mother and fetus. Instead, the paper highlighted the need for tailored management plans, as well as the importance of multidisciplinary care for these high-risk pregnancies. Aguirre Del-Pino et al[15] explored established and emerging risk factors on antiphospholipid antibody (aPL) development and thrombosis. They highlighted how persistent aPLs increase the risk of arterial and venous thromboses and pregnancy complications and how recognizing risk factors for aPL and related thrombosis including genetics, malignancy, infections, and the impact of COVID-19 should be crucial for prevention.

Along with the efforts made in fine-tuning therapy to meet individual patient needs, effective anticoagulation management involves ensuring that appropriate reversal agents are available. We highlight here progress with the

reversal agent andexanet alfa. Several inhibitors of activated factor X (FXa) are currently on the market, including apixaban and rivaroxaban. Andexanet alfa, a modified recombinant form of inactive human FXa, is the only approved reversal agent for patients experiencing uncontrolled bleeding due to apixaban or rivaroxaban. The study from Benz et al[16] suggested it may now be considered for patients with acute major bleeding caused by edoxaban as well. Administration of andexanet alfa in patients on edoxaban was shown to significantly decrease anti-FXa activity and restore hemostatic balance without increasing thrombotic events. The retrospective cohort study by Goldin and colleagues[17] explored real-world practices for administering andexanet alfa to reverse anticoagulation from FXa inhibitors in urgent cases. The authors highlighted a gap in data on andexanet alfa administration and presented findings that could lead to practical changes in clinical management.

Nonetheless, not only thrombosis management is covered by our journals, as they also offer a valuable platform for contributions on bleeding management. This is highlighted by a study from Leebeek and colleagues,[18] which is carried out in adults with von Willebrand disease, an inherited bleeding disorder. The study showed a causal relationship between von Willebrand factor (VWF) activity and spontaneous bleeding events and that exposure of VWF (prophylactic or treatment-related VWF supplementation) reduced the risk of bleeding.

In our effort to meet individual patient needs, understanding and managing the specific risk factors associated with each case is another important publication topic we chose to highlight here.

Challenging Detection Test Efficacy and Risk Factor Considerations

The retrospective cohort study from Khaddam et al[19] compared risk profiles for thrombosis at atypical sites versus typical VTE cases. Distinct patterns of risk were observed, with the F2 20210G > A mutation more common in splanchnic vein thrombosis, and CVST. The findings supported screening for hereditary thrombophilia in atypical thrombosis. Systematic testing or new diagnostic methods do, however, not necessarily guarantee improved outcomes.

Here, we highlight examples where reassessing diagnostic methods may be crucial for thrombosis management. Verstraete et al[20] tackled the significant limitation of thrombophilia testing value in healthy individuals with a family history of VTE and genetic testing for factor V Leiden. They presented three cases of genetic discrimination encountered in outpatient clinic highlighting the need for careful consideration of psychological and social impacts of thrombophilia testing. In a retrospective single-center study, Uzun et al[21] tested the particle gel immunoassay for detecting anti-platelet factor 4 antibodies in patients with vaccine-induced immune thrombotic thrombocytopenia (VITT), a rare complication of adenoviral COVID-19 vaccines. They found rapid test PaGIA to be unreliable for diagnosing VITT due to its low sensitivity and specificity compared to enzyme immunoassay. In a post-hoc analysis, Rolling et al[22] questioned the relationship between presence of circulating tumor cells (CTCs) and thromboembolic events (TEs) in patients with glioblastoma (GBM), a condition that increases the risk of both arterial and venous TEs due to factors like surgery, corticosteroids, radiation, chemotherapy, and the tumor's prothrombotic properties. The study concluded that while GBM patients had a high risk of TE, CTCs were not clearly associated with this risk.

In our effort to refine clinical management and diagnostic strategies for thrombosis, health care is increasingly integrating mobile technologies and artificial intelligence. These innovations have shown promising results and have the potential to complement and enhance existing diagnostic and management routines, potentially informing and updating clinical guidelines.

Integrating Mobile Technology and Machine Learning

Romiti et al[23] conducted a re-analysis of the mAFA-II cluster randomized trial, using the Win Ratio methodology, which offers advantages over traditional methods, particularly for trials assessing composite endpoints. This re-analysis confirmed the previously published results, and highlighted the significant benefits of mobile health technology for improved screening and optimized integrated care in AF. As benefits of mobile apps in health care have been and are continuing to be established, the use of machine learning (ML) is marking a new era for management and diagnosis of health conditions, complementing and possibly outperforming traditional gold-standard diagnostic testing.

Although well established for predicting cancer-associated thrombosis, the Khorana score model shows limitations due to its exclusion of several risk factors and poor performance in some cancer types. The systematic review from El-Sherbini et al[24] evaluated the current use of ML models for thrombosis prediction in cancer patients and found that ML models, particularly the extreme gradient boosting model, surpassed the Khorana score in several datasets. This suggested that ML could provide more accurate risk assessments, though further studies are needed to validate its broad applicability. The narrative review by Franchini et al[25] on catastrophic thrombosis, which is marked by widespread TEs in multiple blood vessels over a short period, also presented a diagnostic and management algorithm to guide clinicians in handling this medical emergency.

On World Thrombosis Day 2024, we reflect on the significant advancements in both the scientific understanding and clinical management of thrombosis, as showcased in our four journals. Through research on thromboinflammation, personalized anticoagulation strategies, and the integration of cutting-edge technologies like mobile health and ML, our community has made strides in improving patient outcomes and reducing the global burden of thrombosis.

Conflict of Interest
G.Y.H.L. is Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Anthos. No fees are received personally. He is a National Institute for Health and Care Research (NIHR) Senior Investigator and co-principal investigator of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 899871.

Acknowledgments
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