Thrombosis and Haemostasis 2020 Editors' Choice Papers

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In this Editor's choice, we highlight last year's papers from *Thrombosis and Haemostasis* as well as from its open access companion journal *THOpen*, which found most resonance among our readers' community, holding promise for mechanistic understanding and improved clinical management in the fields of Thrombosis and Haemostasis. Building on the research investigations from this undoubtedly memorable year may be particularly useful to overcome the current pandemic situation. As it became apparent that coronavirus disease 2019 (COVID-19) was not merely a pulmonary disease but that thrombosis was a key element involved in its severity and complications, the thrombosis research community deployed intensive research efforts in the hope to optimize treatment and/or prophylaxis as well as to decipher the mechanisms and characteristics of COVID-19 thrombosis as rapidly as possible. Due to the urgency of the pandemic development, it was indeed not surprising that publications relating to COVID-19 received by far the most attention in 2020.

Unprecedented Research Efforts for Unprecedented Times

Early on into the pandemic, Lippi and Favaloro[1] proposed the simple D-dimer test for prognosis of COVID-19 severity in a short T&H report which received particular resonance. By using classic coagulation tests together with point-of-care methods such as whole blood thromboelastometry, Spiezia et al[2] further reported specific coagulation alterations, thereby identifying a state of severe hypercoagulability in COVID-19 patients with acute respiratory failure. The systematic review and meta-analysis from Jin et al[3] described the coagulation abnormalities seen in Chinese patients with COVID-19. Boscolo et al comparatively assessed the values of different coagulation tests between patients admitted to internal medicine department versus intensive care unit.[4] Beyond this hypercoagulation state, Violi et al extensively reviewed how clotting variables behave and impact on the severity of COVID-19 along with potential antithrombotic treatment options in COVID-19.[5] Marchandot et al proposed that haemostatic abnormalities could be used to help stage severity of COVID-19.[6]

To help thrombosis specialists, investigators, and funders, a truly multidisciplinary collaborative group of experts in disciplines including cardiovascular diseases, hematology, vascular medicine, pharmacy and pharmacology, pulmonary and critical care medicine, laboratory medicine, and health policy joined efforts to form the Global COVID-19 Thrombosis Collaborative Group. Their position paper[7] comprehensively discussed classical anticoagulants, antiplatelet drugs, and their anti-inflammatory mechanisms and also agents that modulate inflammation and may thus help to mitigate thromboinflammation. While a panel of experts from China and Europe published a consensus statement with practical guidelines for the prevention and treatment of venous thromboembolism (VTE) associated with COVID-19,[8] Grandmaison et al highlighted the benefits of systematic VTE screening in COVID-19 patients.[9] A position paper from the Vas-European independent foundation reaffirmed this in angiology/vascular medicine.[10]

Understanding the mechanism of COVID-19 thrombosis is critical for all efforts toward defining clinical characteristics and optimizing antithrombotic treatment for COVID-19

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patients. In this respect, Cattaneo et al raised an important question regarding the interpretation of thrombotic risk in COVID-19 patients, as they argued that COVID-19-related thrombosis in the lung is due to pulmonary thrombi rather than pulmonary emboli.[11] They further advocated for a role of von Willebrand factor and platelets in COVID-19 pathogenesis,[12] questioning the use of high-dose heparin for COVID-19 patients. Scoring well with Altmetrics, the study from Eriksson et al investigated implications of the complement system in COVID-19 pathology,[13] identifying the mannose-binding lectin pathway as a potential target for antithrombotic treatment and diagnostic in COVID-19 thrombosis. As put forward by the review of Vaughan et al,[14] obesity appears to be another crucial risk factor, which may be independently driving the heterogeneous host response and hyperinflammation driving COVID-19 and its severity. Following the hypothesis that bradykinin is involved in COVID-19 pulmonary edema, the study from Miesbach suggested that angiotensin II was elevated in COVID-19.[15] In a comprehensive review, Gencer et al surveyed the mechanisms that may explain how viral entry and activation of endothelial cells by Sars-Cov-2 can give rise to a series of events including systemic inflammation, thrombosis, and microvascular dysfunction, which is particularly fatal in patients with overt cardiovascular disease.[16] The review shed light on a role of the renin-angiotensin aldosterone system and its inhibitors, and the impact of antiviral and anti-inflammatory treatment options in COVID-19.

As important as it is to address the current needs for optimizing medical treatment, any given strategy will only be successful, if based on a solid foundation of understanding the underlying mechanisms.

Refining Anticoagulation Treatment Choices

Identifying and Treating Thrombosis in a Diversity of Patients

To tackle the multidimensional aspects of atrial fibrillation (AF) and the more complex treatment options available to date, a paradigm shift from classification toward a structured characterization addressing specific domains with treatment and prognostic implications has been proposed by Potpara et al, in alignment with the new 2020 European Society of Cardiology (ESC) guidelines.[17] This 4S-AF scheme sums up the aspects of our initial evaluation and assessment to "characterize" the patient with AF: Stroke risk, Symptoms, Severity of AF burden, and Substrate severity. This is reflected in the new ESC AF guidelines, proposing a structured approach to integrated AF care: "A" Avoid stroke; "B" Better symptom management with patient-centered rate or rhythm control; "C" Cardiovascular risk factor and comorbidity optimisation.[18]

A clinical focus addressed how female sex is a stroke risk modifier rather than a risk factor per se, and cautions against ignoring the additive effect of female sex on risk, given that female AF patients tend to be suboptimally managed and often not offered oral anticoagulation for stroke prevention.[19] The impact of aging and incident comorbidities on stroke risk emphasized by Chao et al[20] was also cited in the new ESC guidelines to remind us that risk is dynamic, and not a static "one off" assessment.

Whether East-Asian AF patients, who may be more prone to bleeding events, should be prescribed lower warfarin international normalized ratio (INR) for stroke prevention, has been a long lasting debate. The thorough meta-analysis from Pandey et al[21] raised concerns about this practice and suggested that a ratio of 2.0 to 3.0 should be adopted overall. Additional high-quality studies, especially prospective and randomized trials, will be necessary to define the optimal range for Asian AF patients.[22,23]

High body weight and obese patients represent another subgroup, for whom the risks associated with anticoagulation treatment remains uncertain. The study by Martin et al was well relayed on social media, as it challenged the International Society of Thrombosis and Haemostasis guidance on routinely checking direct oral anticoagulant (DOAC) concentrations in these patients.[24] The results supported the growing clinical evidence on the efficacy and safety of DOACs in high body weight patients. Additional insights from an ancillary analysis on body weight from the ENGAGE-AF TIMI 48 trial show how patients with low body weight had a more fragile clinical status and poorer INR control; importantly, the pharmacokinetic/pharmacodynamic profile of edoxaban was consistent across extremes of body weight, resulting in similar efficacy compared with warfarin, while major or clinically relevant nonmajor bleeding were most favorable with edoxaban as compared with warfarin in low body weight patients.[25]

In an effort toward improving the balance between benefits and risks of anticoagulation therapy, the already well-cited study by Spyropoulos et al identified elevated D-dimer levels as an indicator to predict increased bleeding risk.[26] Also toward this goal, the tool developed by Harenberg et al[27] could rapidly detect DOACs in urine and could easily be implemented in clinical routine examination of patients with suspicion of a major bleeding. As treatment efficacy as well as reliability of clinical studies rests foremost on the accuracy of the diagnostic, it is particularly important to identify those patients, who fall out of the diagnostic scope. Interestingly, several papers focused on the use of biomarkers for risk stratification in AF, and their nonspecific nature, being reflective of a sick patient or a sick heart.[28,29] The updated systematic review on the association of antiphosphatidylserine/prothrombin antibodies with the autoimmune disorder antiphospholipid syndrome, may help identifying antiphospholipid syndrome patients otherwise negative for current tests.[30] The relevance of clinical conclusions also relies on the strength of the technique used. In this regard, the relevant methodological validation study by Pieters et al[31] demonstrated the impact of different variables on maximum absorbance in plasma and should help investigators to accurately validate fibrin clot formation and structure in plasma.

Dual Pathway Therapy

In our last Editor's Choice,[32] we addressed dual pathway therapy combining antiplatelet and anticoagulant therapy and mentioned the results from the randomized EDOX-APT study investigating the effects of edoxaban, the most recently approved

DOAC for AF, on patients treated with antiplatelet therapy followed by aspirin withdrawal.[33] The results showed that alternative antithrombotic treatment regimens cannot replace the selective effects of aspirin on platelet COX-1 blockade and called for caution on strategies of aspirin withdrawal in the absence of an effective alternative antithrombotic treatment. Dual antiplatelet therapy (DAPT) has to balance ischemic and bleeding risk. The progress in the field of antiplatelet therapy for acute coronary syndrome and percutaneous coronary intervention over the years including strategies to individualise DAPT intensity and duration and de-escalation of DAPT intensity were reviewed in a well-received T&H Historical Series article.[34] Weitz et al further elucidated the rationale of such dual pathway therapy for atherosclerotic diseases.[35]

Thrombosis Association with Other Pathologies

The Caravaggio study, a large trial on the treatment of VTE in patients with cancer comparing apixaban with dalteparin, addressed the issue of thromboembolic complications in cancer. It was included in an updated meta-analysis of randomized controlled trials by Giustozzi et al,[36] which could confirm the efficacy and safety of DOACs compared with low-molecular weight heparin for the treatment of cancer-associated VTE. The meta-analysis by Cavallari et al should also reassure clinicians on the efficacy and safety of DOACs in AF patients with cancer.[37] An analysis of data from the United Kingdom showed as well that the use of oral anticoagulants is not associated with the incidence of cancer overall among patients with AF, although a possible association between DOACs and colorectal and pancreatic cancer may be present.[38]

Patients suffering from renal impairment are at even higher risk of thrombosis and bleeding. In this respect, the analysis of two large studies, the MAGELLAN and MARINER trials, by Weitz et al[39] shed new light on dosing and safety of rivaroxaban in such patients. As successful oral anticoagulation treatment very much relies on adherence, we welcomed the efforts by Hwang et al, who reassuringly confirmed good adherence of oral anticoagulants for AF dosing regimens in real-world practice,[40] highlighting the importance of patient satisfaction in effective clinical management.[41,42]

Aside from Anticoagulation

In some patients with AF where oral anticoagulation is unsuitable for stroke prevention, implanting left atrial appendage occlusion may represent a valid option. A balanced view on the subject was given by Ding et al in an interesting Clinical Focus article.[43]

We also highlighted last year, new laboratory practice suitable for haemophilia A patients on the recently approved bispecific monoclonal antibody emicizumab.[44,45] A timely review by Gelbenegger et al summarized published clinical trials and preliminary reports of promising treatment with emicizumab and discussed its clinical implications.[46] Its cost-effectiveness and budget impact were highlighted by Cortesi et al.[47] Often underestimated, the risk of major adverse limb events is unfortunately very high in patients with peripheral artery disease. Pastori et al[48] reported a well relayed comprehensive meta-analysis to alert physicians on the positive impact of statins for this group of patients.

Underlying Mechanisms and New Targets

Inflammation, Thrombosis and Cardiovascular Implications

The link between inflammation and thrombosis is now well established and targeting inflammation represents a convincing and promising therapeutic approach to prevent thrombosis. The well-received meeting report from the third Maastricht Consensus Conference on Thrombosis[49] provided a comprehensive overview of the state-of-the-art consensus and recommendations on future challenges of thromboinflammation and cardiovascular pathologies, which may inspire new research avenues in the role of inflammatory mediators, cells, and pathways in cardiovascular disease. The implication of B lymphocytes in atherosclerosis was illustrated by a study by van der Vorst et al investigating the role of the CXCL13/CXCR5 axis on immunoglobulin M levels and atherosclerosis development.[50] As monocyte subsets are increasingly recognized as players and biomarkers of cardiovascular inflammation, the characterization of human blood monocytes by Hoffmann et al[51] identifying subset-specific novel markers added a valuable contribution to our understanding of circulating monocyte heterogeneity. In a VTE mouse model of vena cava ligation, Kimball et al[52] demonstrated the role of one specific monocyte subset, that is, the "reparative" Ly6Clo monocytes, in thrombus formation and resolution, suggesting that modulating inflammation may be a potential therapeutic strategy to prevent thrombosis.[53] As the first cells recruited to the site of injury, neutrophils represent another relevant immune cell subset implicated in thrombotic diseases. Stakos et al provided a well-received overview of neutrophils' ability to release neutrophil extracellular traps during thrombosis. Although their antimicrobial effects is beneficial in infectious diseases, their ability to stimulate inflammation can lead to tissue damage and thrombosis, making them novel candidates for diagnostic and therapeutic targets of thrombosis.[54] Targeting the complement system may also prove to be a successful strategy in some thrombotic conditions. In this regard, an interesting study by Gavriilaki et al[55] analyzed genetic susceptibility in patients with transplant-associated thrombotic microangiopathy, supporting the concept that complement regulatory genes play a role in severe thrombotic complications of bone marrow transplant.

Novel Diagnostic and Therapeutic Targets

In an effort to elucidate the precise mechanisms that trigger clotting in venous thrombosis, Tilburg et al[56] characterized its plasma signature in a venous thrombosis murine knockout model using mass spectrometry-based proteomics, thereby establishing a new tool to diagnose such pathologies.[57] Roka-Moiia et al elucidated the differential effects of biochemical agonists versus hemodynamic shear on platelet activation and procoagulant activity, which may have important implications in the diagnosis of thrombosis associated with cardiovascular

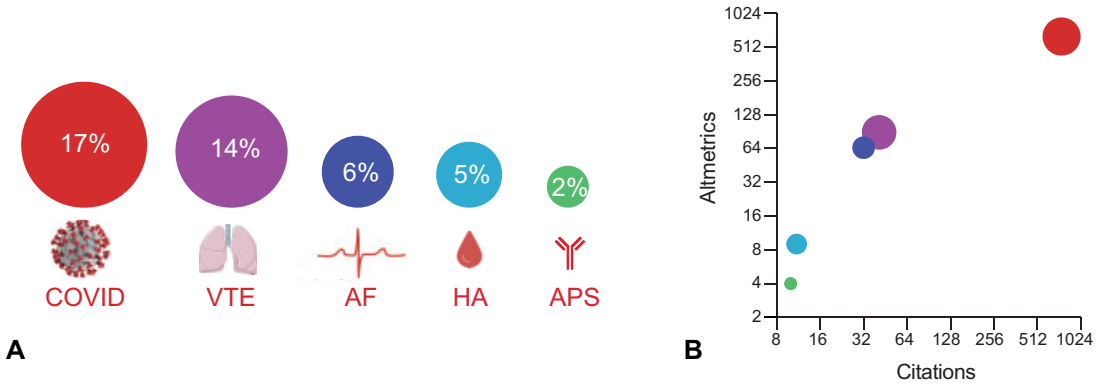

Fig. 1 2020 *Thrombosis and Haemostasis* articles on COVID-19 versus other diseases. (**A**) Percentage of articles published in *Thrombosis and Haemostasis* in 2020 relating to different diseases: Coronavirus disease 2019 (COVID-19), venous thromboembolism (VTE), atrial fibrillation (AF), haemophilia A (HA), and antiphospholipid syndrome (APS). Circle size is proportional to percentage of publications. (**B**) Each group was plotted according to its 2020 total number of citations (*X*-axis) versus Altmetrics score (*Y*-axis).

devices.[58] Albeit the anticoagulation properties of diverse sea cucumber species had already been identified, attempts had failed to isolate its oligosaccharides. Zhou et al[59] achieved this goal, allowing them to comprehensively characterize their individual structures in relation to biological activities. Promising antithrombotic candidates could be identified that exhibited anticoagulation effects without the undesirable stimulatory effects on factor XII and platelet aggregation.

Not unexpectedly, studies that investigated COVID-19 represented a significant amount of publications at T&H last year. Manuscripts on COVID-19 accounted for 17% of articles published in 2020. As a comparison, manuscripts on VTE and AF represented 14 and 6%, respectively (►**Fig. 1**). Not only did COVID-19 studies represent a substantial publication volume but they also ranked top in terms of citations and Altmetrics (►**Fig. 1**). Simultaneously, we have been thriving not to neglect diversity and quality throughout the fields of cardiovascular biology and medicine. We are more than ever looking forward to this New Year by your side and hope it will bring its very much needed share of new scientific insights.

Conflict of Interest

G.Y.H.L. reports consultancy and speaker fees from Bayer, Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo outside the submitted work. No fees received personally.

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