Thrombosis and Haemostasis 2021 Editors' Choice Papers

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This year's Editor's Choice highlights the 2021 manuscripts published in *Thrombosis and Haemostasis* and its open access companion journal *TH Open* that found most resonance within our academic community. As in the precedent year, the 2021 COVID-19 pandemic situation has dictated the pace and direction of our research and clinical management efforts which, although not exclusively, is well reflected by this years' Editor's Choice contents.[1–4]

At the end of 2020, we published a Theme Issue dedicated to COVID-19 as a guide to better comprehend newly identified vascular and inflammatory mechanistic aspects of the disease,[5] its hypercoagulation state,[6] and clinical implications for vascular patients with COVID-19.[7,8] To address the rapidly evolving situation and following a first consensus paper,[9] we were pleased to publish an interesting discussion manuscript by the VAS investigators on the need for a more integrated and global strategy to COVID-19, providing a useful overview of public health approaches consideration and the next steps necessary to best manage the pandemic.[10] While research efforts throughout 2020 focused on characterizing the coagulation abnormalities observed in COVID19 patients giving cues to the next clinical approaches to adopt, the results from such strategies mostly came out in the following year 2021.

Understanding and Managing COVID-19

Anticoagulation for COVID-19

Among the first published anticoagulation results in COVID-19, the cohort study from Billett et al found that patients with moderate or severe disease benefited from anticoagulation and that apixaban had similar efficacy to enoxaparin in decreasing mortality.[11] The large real-life observational CORIST Collaboration study could confirm that heparin lowered in-hospital mortality, particularly in severely ill COVID-19 patients and in those with strong coagulation activation.[12]

The first randomized controlled trial with antithrombotic sulodexide in COVID-19 by Gonzalez-Ochoa et al[13] suggested a benefit of sulodexide in COVID-19 early stage with less frequent hospitalization. Current societal and international recommendations of standard dose thromboprophylaxis in hospitalized patients with COVID-19 were confirmed by the large pooled analysis study from Patell et al.[14] Similarly, the 90-day follow-up of the INSPIRATION Trial[15] supported the routine use of standard dose over intermediate dose prophylactic anticoagulation in intensive care unit patients with COVID-19. Likewise, the multicenter retrospective study of venous thromboembolism (VTE) in COVID-19 patients by Cohen et al[16] endorsed standard prophylactic-dose anticoagulation in hospitalized patients with COVID-19 while individual clinical and laboratory parameters may be instrumental for tailoring thromboprophylaxis strategies in high-risk subgroups. Such high-risk hospitalized COVID-19 patients may indeed benefit from treatment-dose instead of prophylactic- or intermediate-dose low-molecular-weight heparin (LMWH) as demonstrated by the results from the recent multicenter HEP-COVID randomized trial.[17,18] The multicenter observational GeroCovid study, presented convincing data on the role of direct oral anticoagulants (DOACs)

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in reducing the risk of death in COVID-19 older patients.[19] While the beneficial anticoagulation effects of heparin on the thrombotic arm of COVID-19 is easily explicable, intriguing data from Mycroft-West et al suggested that heparin may also prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from infecting cells,[20] opening options for repurposing heparin and its derivatives as antiviral agents.

Importantly, the precise identification of patients, who will best benefit from such prophylactic anticoagulation strategies, is key to their efficacy. Efforts in (re)defining risk biomarkers has therefore been the subject of several studies published last year. As mentioned in last year's Editorial, elevated D-dimer levels were associated with poor prognosis including severity and mortality with COVID-19 infection,[21] making it a biomarker of choice for COVID-19 severity diagnosis. The small retrospective, one center study from Valerio et al[22] further identified specific dynamics associated with D-dimer as well as C-reactive protein levels during COVID-19 which may refine monitoring disease activity. Sjöström et al also proposed a 7-day trend to assess the changing rate of D-dimer and platelet count for dose adjustment in relation to disease severity.[23] Interestingly, Bauer et al pointed out a subtle nature of coagulation changes early in disease progression, highlighting the importance of monitoring coagulation parameters throughout disease progression.[24] Since D-dimer has relatively low specificity and detects only late hemostatic stage, Chaudhary et al laid out the rationale for a study to detect whole blood viscoelastic analysis by thromboelastography or rotational thromboelastometry which may be useful to guide antithrombotic therapy in COVID-19 patients.[25] Several authors[26,27] also systematically analyzed the viscoelastic changes in the clotting system and acknowledged its use for predicting thromboembolic complications and to monitor the efficacy of anticoagulation and fibrinolytic treatment in COVID-19 patients. In a small pilot study, Hardy et al investigated daily monitoring of fibrin-related markers to better detect thrombotic events in COVID-19 patients, and suggested these could be used as further transient warning signals as D-dimers stay constantly elevated in critical patients.[28] In a retrospective study of COVID-19 hospitalized patients, Sweeney et al demonstrated an association of low ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity on admission with increased risk of mortality, providing a further maker to detect patients who may benefit from more aggressive anticoagulation treatment.[29] While clinical efforts to limit COVID-19-induced coagulopathy were and are imminently required in the actual situation, we also welcomed some less sought after strategies which may open new horizons for understanding and treating the hypercoagulation state of the disease. In this respect, Léopold et al shed light on the contribution of platelets to thromboembolic complications encountered in COVID-19 patients as they characterized the platelet phenotype and reactivity to collagen on SARS-CoV-2 infected hospitalized patients.[30] The role of platelets in COVID-19 was also highlighted by Ghirardello et al in a flow-chamber system suggesting impaired platelet activity and thrombus formation in the early phase of COVID-19.[31] Such findings may open new avenues for antiplatelet drugs in COVID-19. Violi et al reported on a case series study of COVID-19 patients with hypoalbuminemia and intravenous administration of human albumin,[32] thereby suggesting an innovative approach to dampen hypercoagulability worth considering. Hemoperfusion devices mimicking the endothelial glycocalyx may represent another option to treat SARS-CoV-2 as shown by a case report from Pape et al.[33] Through electrostatic attraction, such systems are able to capture viruses, bacteria, and cytokines and may potentially reduce viral antigen and cytokine load in the setting of a cytokine storm.

While a great part of our scientific and clinical community has been fully engaged in identifying and refining anticoagulation management strategies for COVID-19, the virology and immunology scientists have been extremely fast in delivering the first efficient vaccines against SARS-CoV-2, creating a blow of hope throughout the world. As it appeared that some rare but severe cases of thrombotic events occurred after inoculation with adenoviral vector-based vaccines, it was crucial that such events should be better understood and treated by the thrombosis community. Although suspended or restricted in many countries, at least 1 billion doses of the adenoviral ChAdOx1 nCov-19 vaccine (AstraZeneca) are currently being released to low- and middle-income countries, making identification and treatment of vaccine-associated thrombosis crucial, as vaccination currently appears to be our sole pandemic exit strategy.

Understanding and Treating Vaccine Complications

In late February last year, rare but severe thrombotic events concomitant with thrombocytopenia, were reported in otherwise healthy individuals shortly after vaccination with the adenoviral vector-based vaccine ChAdOx1 nCov-19 and later with another adenoviral vector-based vaccine (Ad26.COV2.S Janssen; Johnson & Johnson). Risks versus benefits were carefully assessed in a timely consensus paper from experts in the field,[34] who proposed a tracking algorithm for vaccinated patients based on 10-point guideline for safe decision-making. In this novel disorder, termed "vaccine-induced immune thrombotic thrombocytopenia" (VITT), vaccine components appear to form complexes with platelet factor 4 (PF4) on platelet surface triggering formation of high-avidity anti-PF4 antibodies able to activate platelets in VITT patients[35] strongly mimicking immune heparin-induced thrombocytopenia (HIT). In this context, the recently developed humanized monoclonal antibodies tools by Vayne et al[36] to study the antibody response in autoimmune HIT may also help understanding VITT pathophysiology. While similar, HIT and VITT are however not identical[37] and "rapid" PF4/heparin assays have been shown unsuitable to diagnose VITT in contrast to enzyme-linked immunosorbent assay-based PF4/heparin immunoassays.[38] Because these immune complexes bind and activate platelets via Fc gamma receptor IIA, von Hundelshausen et al[39] interestingly advocated for considering off-label use of Bruton tyrosine kinase (Btk) inhibitors (approved for B cell malignancies) in VITT, as

they are expected to target Fc gamma RIIA-mediated activation of platelet aggregation. A proof-of-concept could be indeed provided in a subsequent study showing that Btk inhibitors inhibit platelet aggregation in whole blood induced by VITT serum from patients treated with or without intravenous immunoglobulins.[40]

In addition to thrombosis, other immunological reactions to SARS-CoV-2 vaccines have suggested that autoantibodies against the spike protein S1 of SARS-CoV-2 may be responsible for conditions such as immune thrombocytopenia, vasculitis, Schönlein-Henoch purpura, autoimmune hepatitis, and Guillain–Barré syndrome.[41] Case reports such as that from Farley et al describing[42] a case of acquired hemophilia after SARS-CoV-2 vaccination should therefore be considered carefully. Importantly, all cases reported recovered after adequate treatment, and should not hamper but rather help towards our vaccination efforts by providing transparent communication and defining appropriate treatment.

Refining Anticoagulation Management

Informing the 2020 European Society of Cardiology (ESC) guidelines on atrial fibrillation (AF), the proposal for characterization and evaluation by Potpara et al[43] described the multidimensional aspects of AF requiring moving from classification toward a structured characterization addressing specific domains with treatment and prognostic implications, the 4S-AF scheme: Stroke risk; Symptom severity; Severity of AF burden; and Substrate. Our journal also published the Executive Summary of the 2021 Focused Update Consensus Guidelines of the Asia Pacific Heart Rhythm Society (APHRS) on Stroke Prevention in AF, with a state of the art discussion of the evidence and management recommendations for this common arrhythmia.[44] The APHRS guidelines, in line with the ESC AF guidelines, recommends use of an integrated care or holistic management approach, based on the Atrial fibrillation Better Care (ABC) pathway[45] to improve outcome in the Asian AF population. The components of the ABC pathway are as follows: "A": Avoid stroke with anticoagulation, that is, well-managed warfarin (time in therapeutic range [TTR] $>$ 65–70%) or non-vitamin K antagonist oral anticoagulant; "B": Better symptom management with patient-centered symptom-directed decisions for rate or rhythm control; and "C": Cardiovascular risk and comorbidity management as well as lifestyle changes. The APHRS guidelines noted evidence from a systematic review and meta-analysis of $>$ 285,000 patients from different regions of the world (including Asia), showing how adherence to the ABC pathway is associated with a markedly lower risk of all-cause death, cardiovascular death, stroke, and major bleeding, as well as hospitalizations.[46] Of note the integrated care approach can be applied to other clinical scenarios (e.g., stroke, aortovascular disease) given the need to manage the "whole" patient, and not just one aspect of the patient.[47,48] Before characterization and treatment of AF, it is important to detect the arrhythmia given the potential impact on clinical outcomes.[49,50] Indeed, even asymptomatic AF is not benign, as shown in a nice study of the risk of ischemic stroke in asymptomatic AF patients incidentally detected in primary care.[51,52] Kitsiou et at[53] put forward the importance of continuous cardiac monitoring for detecting AF after a stroke, enabling clinicians to promptly switch to oral anticoagulation and prevent new strokes. Nelson et al addressed the existing literature on different anticoagulation strategies efficacy for critical care patients with AF, pointing out to our urgent need for randomized trials with standardized outcomes for such patients.[54] Machine-learning approaches which account for risk factors' dynamic nature and multimorbidity may improve clinical stroke risk assessment over clinical scores, as demonstrated by a comparative study based on a large real-world data set.[55] Jones et al investigated the economic aspects of service interventions and put into light the cost-effectiveness of anticoagulation clinics, in particular targeting patients at high-risk and/or with suboptimal treatment,[56] a subject less often studied but nonetheless crucial in improving management praxis. While we require to acknowledge the dynamics of stroke risks and implement management flexibility accordingly, identifying specific groups of patients whose risks and benefits need to be weighted, also determines the success of anticoagulation strategies. Indeed, a balance between simplicity, practicality, and clinical application is needed. Biomarker-based scores can be nonspecific (predicting adverse events beyond stroke and bleeding), and more complex clinical scores are not necessarily the answer given that statistical significance is not the same as clinical significance.[57,58]

In our last Editor's Choice, we mentioned the difficulty in assessing risk–benefit tradeoff of antithrombotic therapies in East Asians patients who are more prone to bleeding. An interesting analysis by de Vries et al showed why event rates are higher in clinical practice than randomized trials of stroke prevention in AF.[59] Also, Pandey et al published a systematic review and meta-analysis comparing lower versus standard international normalized ratio (INR) targets in AF, showing evidence that low INR targets may be associated with lower bleeding but has more adverse outcomes.[60,61] This work informed the 2021 APHRS guidelines on AF, and highlights the importance of standard targets and good quality anticoagulation control, with high TTR. The consensus document from Kim et al on the safety and efficacy of different antithrombotic agents in Asians compared with Caucasian patients was welcomed by the clinical community as reflected by its high citation score.[62] How AF patients with intermediate risk can benefit from anticoagulation is an important issue, which was addressed in a nationwide population-based study by Choi et al[63] who observed benefits appear to have an age threshold. Also, some "real-world" evidence on the timing of starting oral anticoagulation, after an acute ischemic stroke with AF was provided by Chang et al, who showed the potential for more bleeding if anticoagulation was started early.[64] Although risks associated with anticoagulation treatment in high body weight and obese patients is uncertain, the International Society of Thrombosis and Haemostasis guidance requires routinely checking DOAC concentrations in these

patients which was challenged by two studies published last year[65–67] that confirmed that almost all high body weight patients achieve expected drug levels with the use of apixaban, edoxaban, and rivaroxaban with no compromise in efficacy. Patients who suffered from major hemorrhage represent another group for whom the benefits and tradeoffs of anticoagulation remain uncertain.[68] Although it seems natural to fear bleeding more than thrombosis in patients after major hemorrhage, Milling et al challenged this bias as they observed net benefit with restarting anticoagulation in a post hoc analysis on the DOAC reversal study ANNEXA-4, highlighting the need for randomized clinical trials in major bleeding scenarios.[69] The well relayed consensus document from Douxfils et al[70] also provided useful updated International Council for Standardization in Haematology guidance for laboratories regarding timing and modalities of monitoring DOACs, now including the newly Food and Drug Administration-approved DOAC betrixaban, and the specific DOAC reversal agent andexanet alfa. In our 2020 Editor's Choice we also highlighted reassuring evidence on the safety of DOACs in cancer patients,[67,71–73] an issue again discussed by Falanga et al last year.[74] The Swedish Patient register cohort study confirmed current AF guidelines on DOACs originally aimed for the general AF population.[75] Supporting evidence also came from a study from Cohen et al[76] among patients with VTE and active cancer prescribed apixaban, LMWH, or warfarin. In a post hoc analysis of the Caravaggio study, a large trial on the treatment of VTE in patients with cancer comparing apixaban with dalteparin, Ageno et al[77] reported additional data on bleeding events which supports administering apixaban to an even larger population of cancer patients than previously recommended by guidelines, also including patients with gastrointestinal cancer, and should help clinicians translate the findings of the CARAVAGGIO study into clinical practice. Pregnancy and the postpartal phase are also associated with increasing VTE risk making it a leading cause of maternal mortality. We therefore very much welcomed the insights from the Global Anticoagulant Registry in the FIELD (GARFIELD)-VTE into the clinical characteristics, diagnostic strategies, treatment patterns, and outcomes of women with pregnancy-associated VTE.[78] To refine bleeding risk for VTE patients under anticoagulant therapy, a valuable study compared the "classic" Registro Informatizado de Enfermedad TromboEmbólica (RIETE) score to the more recently developed VTE-BLEED score at different times after VTE diagnosis, with similar results for the prediction of early and late bleeds, and only small differences depending on the time since VTE diagnosis and the site of hemorrhage.[79] As autoimmune hemolytic anemia is increasingly recognized as a strong risk factor for venous thrombosis but there are not yet any guidelines on thromboembolism prevention and management in this context, case report studies such as that of from Solari et al should prove very useful to the clinical community.[80] Cirrhosis represents another disorder often associated with splanchnic vein thrombosis for which the meta-analysis from Valeriani et al reviewed useful clinical information on the value of anticoagulation therapy to lower the thrombotic burden without increasing overall bleeding risk.[81] The efforts from Sokou et al[82] to develop an easy-to-use risk score for critically ill neonates based on bed-side assessment of global coagulation and routinely available parameters was most welcome as these subjects have a high bleeding risk difficult to predict with conventional coagulation assays.

Following the ESC guidelines on acute coronary syndrome, the state-of-the-art review by Guedeney and Collet provided a comprehensive overview of current evidence on the pharmacological management of patients with acute coronary syndrome, particularly on the use of modern and more potent antiplatelet agents.[83] The risk–benefit tradeoff of antithrombotic therapies in East Asian patients was informed by the pharmacodynamic randomized trial A-MATCH which evaluated a prasugrel deescalation strategy in East Asian patients with acute coronary syndrome and showed a higher chance within the therapeutic window with reduced bleeding episodes.[84]

Bleeding Risks and the Management of Bleeding Complications

Hemophilia A patients whose lack of coagulation factor VIII (FVIII), put them at risk of prolonged bleeding are conventionally treated with FVIII infusion which is unfortunately limited by the development of neutralizing antibodies. The fourth generation rFVIII product simoctocog alfa (Nuwiq; Octapharma) replicating the native human FVIII protein without incorporation of potentially immunogenic elements of animal cell origin may represent a promising candidate to overcome this issue as reflected by the final data of the NuProtect study.[85] The recently approved bispecific monoclonal antibody emicizumab represents another very attractive approach for treating hemophilia A patients bypassing FVIII activation. We highlighted last year the published promising clinical trials and preliminary reports with emicizumab[86] as well as its cost-effectiveness and budget.[87] We were pleased to publish new data from the Haven 1 study concerning pharmacokinetic and pharmacodynamic of emicizumab effects[88] which should help the increasing number of clinicians using this new therapy. Severe bleeding is also one of the most common complications for cirrhosis patients with low fibrinogen for whom it is common practice to transfuse blood products such as cryoprecipitate. Budnick et al demonstrated the inefficacy of such treatment in improving survival or bleeding complications, seriously questioning routine management.[89]

Identifying New Targets and Mechanisms

Refining our understanding of platelet procoagulant physiology and pathophysiology has been an active subject of investigation in the context of COVID-19[30,31,35] but also in a more general context as portrayed by further very welcomed investigations last year. Aliotta et al[90] elegantly investigated ion fluxes in collagen and thrombin activated human platelets providing novel insights into the dichotomous role of the sodium–calcium exchanger in procoagulant platelet

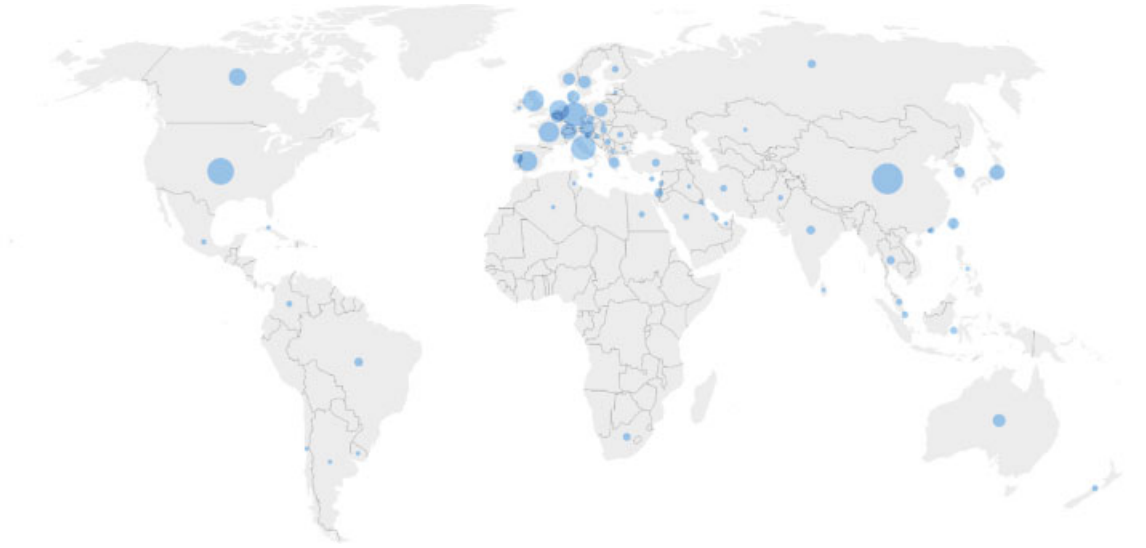

Fig. 1 Worldwide author distribution of original manuscripts submitted in 2021. Circle size is proportional to the total number of original manuscripts submitted in each country. Map created with Datawrapper.

formation. Ya et al have addressed the counteracting effects of protocatechuic acid on the apoptotic PI3K/Akt/GSK3β signaling pathways in human platelets,[91] thereby highlighting a potentially important protective role in the progression of cardiovascular disease. The role of lipid rafts in cyclic adenosine monophosphate signaling homoeostasis in platelet was confirmed by Belleville-Rolland et al[92] who further pointed out to the role of transporter multidrug resistance protein 4 in particular, and thus a new potential target for antithrombotic agents. The importance of the platelet–neutrophil feedback loop was evidence by a case–control study[93] that put forward the importance of combining biomarkers of NETosis and platelet activation to predict the risk of major adverse events in a cohort of postmyocardial infarction patients. NETosis markers may also predict placenta-mediated complications in pregnancy as suggested by a pilot study, derived from the GrossPath study, demonstrating distinct circulating nucleosome-bound histones were increased in complicated pregnancy.[94] Further shedding light on the effect of neutrophil extracellular traps on coagulation, Locke and Longstaff[95] published an interesting manuscript demonstrating the inhibitory effects of histones on fibrinolysis, suggesting new therapeutic targets for preventing thrombosis. Increasing evidence suggests that circulating micro-ribonucleic acids (miRNAs) could be used as diagnostic biomarkers and may even represent therapeutic targets for cardiovascular diseases. The study from Stojkovic et al assessing the relationship between different circulating miRNAs and monocyte-platelet aggregate formation in patients with acute coronary syndrome on dual antiplatelet therapy is an example of such new interest.[96] Garcia et al identified an important role of a specific miRNA, miR-204–5p, on in vitro platelet production and function,[97] suggesting genetic control of platelet production and function by miR-204–5p which may thus be considered as a new biomarker for high platelet reactivity in the context of personalized antiplatelet therapy.[98] The comprehensive overview of currently available techniques for studying miRNA function with a focus on platelet reactivity regulation by Garcia et al,[99] also attracted much interest among our author community seeking to overcome the current methodological limitations in this field.

We are thereby delighted to publish an ever more diverse panel of scientific advances and clinical pictures reflecting the multifaceted aspects of *Thrombosis and Haemostasis*. This past year has brought its share of much needed investigations in understanding and treating the cardiovascular complications associated with COVID-19 in particular, but also in refining current clinical management in thrombosis in a more general context, opening new avenues for targeting and biomarker strategies as well as understanding underlying cardiovascular mechanisms. We are pleased that manuscripts are being increasingly submitted from all over the world: China now holds the record of submissions, followed by the United States, Italy, and Germany (►**Fig. 1**).

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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