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Recent highlights on thrombosis and hemostasis from the International Journal of Cardiology: Heart & Vasculature

1. Covid-19 – Tiny entity, enormous challenge

The early 2020's will undoubtedly be associated with the global crisis that ensued with the spread of the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Daily life stopped still, research and development in fields other than infection and immunity largely halted, and healthcare practitioners and clinicians faced hitherto unknown challenges. It soon became clear that COVID-19 can impact detrimentally on multiple organ systems and exacerbate pre-existing complications. A number of distinct cases of COVID-associated hemostatic derailment with fatal consequences were reported in this journal. Ali et al. [1] described a novel arteriovenous coagulopathy termed *acute COVID-19 induced fulminant systemic vascular thrombosis* (ACoFSVT). A 74-year-old male with history of diabetes developed a rapid, massive and widespread coagulopathy that was very difficult to treat with empiric anticoagulation. Heparin administration was delayed for fear of thrombocytopenia, but derailment of normal hemostatic mechanisms and exhaustion of endogenous anticoagulant factors were suspected to have prompted unopposed clotting activation and widespread vasculopathy and thrombosis. The patient was ultimately transferred to comfort care. Shereef et al. [2] presented the case of a 64-year old female who developed acute limb ischemia and stroke as a complication of a COVID-19 infection. In this case, a pre-existing multimorbidity - encompassing hypertension, hyperlipidemia, morbid obesity, hypothyroidism and prior ovarian cancer - provided the ideal substrate for an overwhelming prothrombotic response to the SARS-CoV-2 infection. Despite full-dose anticoagulation, expanding cerebral ischemia with hemorrhagic conversion led to neurological deterioration that finally placed the patient into comfort care. The hemostatic derailment precipitated by COVID-19 proved a major challenge also for the management of the approximately 20 % of patients who developed in-hospital atrial fibrillation (AF). Gawalko et al. [3] provided a comprehensive overview of the available data on the prevalence and molecular mechanisms of AF in the context of COVID-19, and outlined potential options for acute and long-term treatment Two years on, the long-term impact of COVID-19 after recovery from the acute infection was neatly assessed by a comprehensive *meta*-analysis performed by Ogungbe et al. [4] encompassing 62 articles published during December 2019-August 2021 and including over 41,000 patients. Infection with COVID-19 was associated with severely increased rate of myocardial damage and coagulopathy, raising clear implications for long-term cardiovascular health. Of note, while a large proportion of the patient pool exhibited pre-existing comorbidities (hypertension was present in 39 %, diabetes in 21 %, coronary artery disease in 13 %, chronic obstructive pulmonary disease in 7 % and history of cancer in 5 % of all patients), a large number of patients were considered healthy. The propensity-matched assessment of outcome in COVID-19 patients with new-onset versus prior AF just published in this journal by Cutler et al. [5] also spotlighted COVID-19 as a new-age driver of cardiovascular risk. The adverse impact of in-hospital new-onset AF acquired during a COVID-19 infection on clinical outcome was comparable to that seen in patients with manifested AF prior to infection. The implication is that even patients considered healthy require stringent monitoring for cardiovascular and thrombotic complications during and after COVID-19 infection. The recent multicenter cohort study by Offerhaus et al. [6] identified males aged 60–72 years as a particularly at-risk group. Most important, even vaccination against COVID-19 soon proved to bear a health risk for subsets of patients receiving certain COVID-19 vaccines. Reports of increased rates of microthrombi and myocarditis following vaccination caused substantial and ongoing insecurity in the medical and general populations. Tedeschi et al. [7] reported the case of a 74 year-old female patient who developed Takotsubo Syndrome (TTS), a form of stress cardiomyopathy, within hours of vaccination with a first mRNA vaccine. The patient had no history of SARS-CoV2 infection and no reported current emotional or physical stress. The incidence and severity of TTS associated with COVID-19 vaccines was systematically assessed by Khalid Ahmed et al. [8] The authors concluded that post-vaccination TTS occurs rarely, but if it does can be life-threatening, and recommend monitoring for chest pain as the leading symptom.

2. Steps towards optimised antithrombotic treatment

Meanwhile the controversial discussion regarding optimal antithrombotic strategies – which patients, with which drugs in which combinations, and when to initiate and for how long to continue – went on, with avid participation in this journal. Particularly patients dually afflicted with AF and acute coronary syndrome (ACS) represent a therapeutic challenge, given the amplified bleeding risk associated with dual and triple therapy approaches. In their review, Galli et al. [9] critically appraised the trials and *meta*-analyses comparing double vs triple antithrombotic therapy in patients with AF and ACS requiring percutaneous intervention (PCI). The authors systematically dissected the design and limitations of the individual studies, to cautiously conclude that triple therapy should be preferentially considered during the first weeks after PCI followed by dual therapy thereafter, to account for the increased early in-stent thrombosis that detracts from the net lower bleeding risk with dual therapy approaches. Brunetti et al. [10] followed with a fresh *meta*-analysis of patients with non-valvular AF requiring PCI placed on warfarin or a direct oral anticoagulant (DOAC), plus either single or dual antiplatelet therapy (SAPT, DAPT). Notably the authors carefully considered how the recently published AUGUSTUS and ENTRUST-AF PCI studies impacted on the state of the art. The major

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finding was that DOAC use consistently led to lower bleeding rates than warfarin, with comparable effects on cardiovascular risk and mortality, and that safety and efficacy was similar for DOAC + SAPT and DOAC + DAPT in this cohort with AF patients undergoing PCI. Uncertainties regarding the choice of DOAC + SAPT remain, however, with mounting evidence validating the concern of inadequate ischemic risk reduction. Riesinger et al. [11] presented the design and objectives of the APPROACH-ACS-AF (*APixaban* versus *PhenpRocoumon: Oral Anti-Coagulation plus antiplatelet tHerapy in patients with Acute Coronary Syndrome and Atrial Fibrillation*) trial, which seeks to test the superiority of the dual DOAC-based antithrombotic strategy in terms of bleeding when compared to a guideline-conform triple regimen encompassing warfarin plus DAPT.

Two publications in this journal highlighted further aspects of DOAC superiority over warfarin. Akhtar et al. [12] called attention to osteoporosis as a neglected co-morbidity that frequently complicates AF in elderly patients. Long-term use of warfarin was proposed to amplify osteoporosis via a number of vitamin K-dependent mechanisms, which could be circumvented by DOAC. The letter by Akhtar et al. and the associated editorial by us [13] discussed this underestimated safety advantage of DOAC over warfarin in the context of the current literature. Navarro-Almenazar et al. performed a multicenter retrospective analysis of morbidly obese patients anticoagulated for AF [14]. The authors pointed out that morbidly obese cohorts were not represented in the major landmark DOAC trials, and sought to assess if the favourable efficacy and safety profile of DOAC also holds true in this selected patient population. Reassuringly, the authors found no significant difference in terms of mortality, ischemic stroke, and major bleeding between the high risk morbidly obese group and the general patient population under DOAC treatment. The accompanying editorial [15] discussed the potential mechanistic background, the clinical implications and the gaps in knowledge in this important context.

The selection of appropriate antiplatelet drugs also remains a big clinical challenge. Alfredsson et al. [16] performed an observational study comparing bleeding rates in patients with ST-elevation myocardial infarction (STEMI) who received aspirin plus either clopidogrel or the more potent ticagrelor. The authors highlighted a doubled rate of bleeding over 6 months follow-up in the ticagrelor group. Although the majority of the bleeds were not severe, the more aggressive antiplatelet approach led to more TIMI, PLATO major and BARC $\geq$ 2 bleeding events, without offering additional benefit in terms of death, new MI or stroke risk reduction. In a dedicated editorial [17] we discussed the distinct pharmacokinetic and pharmacodynamic aspects of the two approaches, and the potential implications of this study for individualized therapeutic management.

3. Evolving concepts for risk prediction and scoring

The PRECISE-DAPT (*predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy*) score identifies bleeding risk by considering age, leukocyte count, hemoglobin level, creatinine clearance, and history of spontaneous bleeding. A score of $\geq$ 25 selects patients at high risk of bleeding and for whom guidelines accordingly recommend shorter DAPT duration. Ando et al. [18] proposed the application of the PRECISE-DAPT also for long-term risk assessment after AMI. The authors stratified consecutive acute MI patients according to PRECISE-DAPT low (<17), intermediate (17–24) and high $\geq$ 25 scores. Over long-term follow up (mean 1424 days), higher PRECISE-DAPT score incrementally increased overall mortality, with a strikingly steep rise in all-cause deaths in the high score group. Multivariate assessment adjusting for potential confounders revealed the PRECISE-DAPT score as an independent prognostic factor for long-term mortality after AMI. Dannenberg et al. [19] further expanded the predictive utility of the PRECISE-DAPT score to TIMI bleeding and major adverse cardiac and cerebrovascular events (MACCE) during one-year follow-up after PCI. The authors here compared PRECISE-DAPT score $<$ 25 versus $\geq$ 25. The high score group consistently showed a higher bleeding rate as expected, but also exhibited increased risk for MACCE and the individual components MI and all-cause death. The authors carefully compared the validity of the PRECISE-DAPT with other conventional scores, and critically evaluated their findings and study design, concluding with cautious recommendations for the application of this objective and useful scoring tool.

Kim et al. [20] developed and validated a new model to concomitantly define in-hospital mortality and bleeding risk, in order to better guide early decision-making post MI. Baseline variables associated with MACCE were extracted from the Korean Acute Myocardial Infarction Registry (KAMIR) – National Institutes of Health (NIH) database, of which seven found consideration in the final KAMIR-NIH risk model: age, Killip class, systolic blood pressure, heart rate, serum glucose, glomerular filtration rate, and initial diagnosis. The model was subsequently validated for comprehensive risk stratification for in-hospital mortality and major bleeding.

A novel score to define and stratify stroke risk in patients undergoing catheter ablation for AF was proposed by Chen et al. [21]. The authors pointed out that the $CHADS_2$ and CHA_2DS_2-VASc scores that are conventionally used to identify stroke risk are subject to substantial variability depending on status under ablation. The elegant study design included a propensity-score matched cohort and a validation AF cohort to which a novel model-based scoring system was applied to predict stroke risk. The AF-CA-Stroke score was based on six clinical variables including various age stratifications and catheter ablation status. The adapted score was validated to predict 1, 5 and 10 year-stroke risk with significantly higher decimation than conventional scoring systems.

An additional marker for MACCE and all-cause mortality to be potentially considered in evolving concepts of risk assessment is the soluble fibrin monomer complex (SFMC), as proposed in this journal by Yoshihisa et al. [22]. As comprehensively detailed in the study and discussed in the accompanying editorial [22–23], SFMC could be implemented as an early sentinel for a pre-coagulant state and predictive biomarker in patients with heart failure. An innovative method for SFMC quantification was presented, coupling immunoturbidity with coagulometry to allow measurement of serum proteins not detectable with conventional clinical chemistry methods. Advancement in the diagnosis of left atrial thrombi in patients with persistent AF was provided by Tanaka et al. [24] in the form of a new algorithm. They developed and validated a reliable algorithm based on parameters obtained from cardiac CT: the Hounsfield unit (HU) density at the proximal (p) and distal (d) LA appendages was determined and evaluated as ratio LAAd/LAAp and as standard deviation of HU density (HU-SD) at the LAAd. The diagnostic accuracy of this algorithm was 0.95.

4. Outlook

The International Journal of Cardiology: Heart & Vasculature increasingly serves as a forum for innovative advances in understanding of cardiovascular disease pathophysiology, diagnosis and treatment, and risk prediction. The potential link between thrombo-inflammation, cardiomyopathies, and cardiac diseases is under extensive investigation. The ongoing COVID-19 pandemic and its detrimental long-term impact continue to provide not only challenges in this regard but also opportunities for scientific and medical advancement, while innovations in imaging and biomarker detection will improve individual risk prediction and management. We are looking forward to presenting these and other highlights in the upcoming issues of the journal.

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Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

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