Thrombosis and COVID-19: Controversies and (Tentative) Conclusions

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Infection with SARS-CoV-2, initially isolated to one location in early 2020, rapidly spread to become a global pandemic. In early reports, patients with COVID-19 were noted to have multiple coagulation test abnormalities, including elevated D-dimer levels, and increased thrombotic events (1, 2). These complications have been attributed to "thromboinflammation", a process in which innate immune responses and inflammation trigger coagulation, and endotheilialitis (3), a result of infection of endothelial cells with SARS-CoV-2. Severity of inflammation has been associated with extent of coagulation test abnormalities: for example, higher IL-6 levels are correlated with increasing fibrinogen levels (4). Autopsy studies, first from China and then from Europe, found microvascular thrombosis in patients with COVID-19; these clots were initially thought to be confined to the lungs but were subsequently found in other organs including the heart and kidneys (1, 5). Microvascular thrombosis may, in turn, lead to hypoxemia, organ failure, and death. The thromboinflammatory response to SARS-COV-2 infection and endothelialitis have been proposed to be driving arterial and venous large vessel thrombosis as well as microvascular thrombosis in people with COVID-19 (Figure).

What is the rate of thrombosis in people with COVID-19? The answer to this seemingly straightforward question has been controversial. One early report from China noted a 25% thrombosis rate in critically ill patients (6), prompting use of prophylactic dose low molecular weight heparin (LMWH) for hospitalized patients, a practice that was not standard of care in Asian countries as the baseline risk of thrombosis in the population is lower than in Europe countries and the US (7, 8, 9). Subsequently, in a retrospective study, use of heparin for venous thromboembolism (VTE) prophylaxis was found to decrease thrombosis in critically ill patients (10). Studies from the Netherlands (11, 12) demonstrated increased incidence of venous and arterial thrombosis in patients who were critically ill with COVID-19. In France, patients in the intensive care unit (ICU) with COVID-19 acute respiratory distress syndrome (ARDS) were found to have higher rates of symptomatic VTE than similarly ill ICU patients with non-COVID-19 ARDS (historic controls) (13). In another study, rates of symptomatic pulmonary emboli were 20.6% in mechanically ventilated patients with COVID-19 compared to 6.1% in ICU patients with similar characteristics from the year before and 7.5% in a cohort of mechanically ventilated patients with influenza (14). In these European studies, standard dose VTE prophylaxis with heparins was used. Findings from the US are similar, with high rates of thrombosis reported especially in ICU patients (15, 16). Based on these data, particularly in patients who are critically ill because of COVID-19, some centers began using doses of anticoagulants higher than standard prophylaxis in an attempt to improve clinical outcomes.

With this backdrop, the findings by Dalager-Pedersen and colleagues in *Clinical Infectious Diseases* showing a much lower rate of VTE are particularly striking (17). This study assessed the rate of thrombotic events in two cohorts: one drawn from a nationwide population-based registry of people in Denmark and the other from a more detailed curation of electronic health records (EHR) of all patients with COVID-19 hospitalized at 6 academic centers. In the nationwide registry, rates of thrombosis in patients with positive tests for COVID-19 (16% of whom were hospitalized) were compared with COVID-19 negative patients (12% of whom were hospitalized) and with a historic cohort of patients with influenza (59% of whom were hospitalized). At a population level, the rate of VTE in people with COVID-19 was similar to that of people without COVID-19 and those with influenza (0.4%, 0.3%, and 1.0% respectively). Risks of VTE in the 582 hospitalized patients with COVID-19 in the EHR cohort were higher: 4% in ward patients and 7% in ICU patients. Major bleeding rates in the registry cohort was similar for those who were COVID-19 positive, those who did not have COVID-19, and those with influenza (2.3%, 4.5% and 2.4%, respectively); the rate of major bleeding was highest in the EHR cohort who were critically ill (11%).

This study has considerable strengths – including a large sample size in the nationwide cohort and a comparison group of people without COVID-19 – and an important message, namely that VTE rates may be lower than previously reported. However, Dalager-Pedersen and colleagues acknowledge the study's limitations, some of which reflect challenges faced globally by all investigators trying to collect data in the face of an overwhelming pandemic. These limitations include the fact that over the course of the study, which ran from January to June 2020, Danish national guidelines for anticoagulation dose changed; unfortunately, specific data on anticoagulation dose for those in the national registry cohort were not available. In addition, the evolution in testing and medical care – including use of antivirals, anti-cytokine therapies and other immumomodulators -- is not discussed. The proportion of patients requiring ICU care in the EHR cohort (23%) was lower than what we experienced in the US: at one of our institutions, 48% of the first 210 patients admitted with COVID-19 required ICU care and 86% of these were mechanically ventilated (15).

What accounts for the lower rate of VTE in this study as compared with others? As demonstrated in a meta-analysis of VTE risk in patients with COVID-19, different radiologic imaging strategies markedly affect the prevalence of VTE. In the meta-analysis, the overall prevalence of VTE was 14.1%

(18). Not surprisingly, use of screening lower extremity ultrasound and disease severity influence the rate of diagnosed VTE: in ICU patients, the rate was 18.7% with no screening compared to 45.6% with screening; in non-ICU hospitalized patients the prevalence was 5.5% without screening and 23% with screening. Of note, the use of imaging in the study by Dalager-Pedersen et al was low, with only 13% of the EHR cohort imaged with CT, 1% with ventilation-perfusion scans, and 3% with lower extremity ultrasound.

In addition to the possibility of ascertainment bias, other factors may markedly influence results from different studies, leading to controversy and confusion. When calculating VTE incidence, crude rates may not account for the competing risk of mortality. Retrospective data from single centers are prone to bias. There are variations between studies in the definitions of VTE, major bleeding events, and COVID-19 severity. And finally, over the course of the pandemic and in different regions, there has been heterogeneity in criteria for SARS-CoV-2 testing, threshold for hospital admission and ICU care, and the interventions used to treat COVID-19, all of which may influence VTE rates. Going forward, standardized definitions, measurements and analytic approaches are needed to make progress.

Indeed, with ongoing surges in new cases of COVID-19 around the world, and with new SARS-CoV-2 variants that might change the trajectory of the pandemic, there is a critical need for accurate data on VTE incidence to guide care. Early treatment decisions on anticoagulation intensity were based on initial reports of VTE event rates and local experience. In fact, guidelines for anticoagulant dose have been mixed in their messaging: while most support the use of established or standard dose anticoagulants for VTE prophylaxis (American Society of Hematology https://www.hematology.org/covid-19 ; American College of Chest Physicians (19)) others note that 30-50% of members support use of intermediate intensity dose, or dose based on weight, D-dimer, and severity of illness (American College of Cardiology (20) International Society on Thrombosis and Haemostasis (21) Royal College of Physicians https://www.nice.org.uk/guidance/ng186/chapter/1-Patients-with-COVID-19-pneumonia-managed-in-hospital) Anticoagulation Forum (22)).

The goal of anticoagulation in COVID-19 is to prevent macrovascular venous and arterial thrombosis, with the hope of mitigating the devastating effects of microvascular thrombosis (Figure). There is significant variation in practice from center to center, usually with higher dose strategies for those

admitted to the ICU, despite lack of definitive data for efficacy and safety in people with COVID-19. Given the bewildering array of anticoagulation strategies that are being used, how are we to make progress in this critical area of care? Clearly, the best way forward is to conduct and complete randomized controlled trials (RCTs) rather than relying on often conflicting data from single center non-randomized studies. At present many anti-thrombotic clinical trials are underway around the world, evaluating different intensities of anticoagulation from standard dose used for prophylaxis to full therapeutic dose; some studies also include antiplatelet agents (https://www.clinicaltrials.gov/ct2/results?cond=covid-19+and+anticoagulation&term=&cntry=&state=&city=&dist=; accessed January 24, 2021).

The critical importance of randomized controlled trials to lead us from controversy to conclusions is highlighted by rapidly evolving information from three clinical platform trials being conducted around the world. In recent weeks, enrollment of critically ill patients was halted into the therapeutic dose anticoagulation arms of the ACTIV-4 Antithrombotics Inpatient, REMAP-CAP, and ATTACC trials based on findings of futility to prevent 21 day organ free support; of note, a potential for harm in this subgroup could not be excluded (https://www.nih.gov/news-events/news-releases/nih-activ-trial-blood-thinners-pauses-enrollment-critically-ill-covid-19-patients). By contrast, in moderately-ill hospitalized patients (those not in intensive care and not receiving organ support), interim results are that therapeutic dose anticoagulation is superior to prophylactic dose anticoagulation at reducing need for ventilation or other organ support (https://www.nih.gov/news-events/news-releases/full-dose-blood-thinners-decreased-need-life-support-improved-outcome-hospitalized-covid-19-patients). If borne out when more information is available, these findings suggest there may be a "window of opportunity" during which anticoagulation makes a difference: moderately-ill hospitalized patients may benefit from therapeutic anticoagulation whereas critically ill patients may need other interventions, perhaps because the window of opportunity to prevent thrombotic omplications has closed. Clearly, more information (beyond press releases) is needed from these and other studies before drawing this conclusion. Moreover, as illustrated by the low rate of thrombosis in the study by Dalager-Pedersen et al, knowing who is at greatest risk for clinical complications is critical to informing ongoing and future clinical trials.

Despite the importance of these studies, however, we will need more than anti-thrombotics to optimally treat COVID-19. Multiple processes associated with COVID-19 can contribute to activation

of coagulation, and thus a multi-pronged approach is likely to be best (Figure). The limitation associated with increasing doses of anticoagulants is the increasing risk of bleeding, which is exacerbated by ICU care and attendant complications. Therapeutic anticoagulation may improve outcomes in moderately-ill hospitalized patients but may be too late to benefit people with hypoxemic respiratory failure. In addition, there is the question of timing: randomized trials of antithrombotics in ambulatory patients with COVID-19, such as ACTIV-4 Outpatient Thrombosis Prevention Trial (NCT04498273), should answer the question of whether sooner is better than later. Multiple simultaneous strategies are likely to be needed to combat the effects of SARS-CoV-2 infection, including antiviral agents, immumomodulatory therapies, and anticoagulants, depending on the stage and severity of disease (Figure). It will only be through global collaboration and randomized controlled trials that we will settle the controversies and arrive at definitive conclusions on how best to prevent and treat thrombosis in people with COVID-19.

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Figure legend: Thromboinflammation in COVID-19 and Potential Sites for Intervention

The innate immune system and the coagulation system are the two major engines for thromboinflammation. SARS-CoV-2 infects endothelial cells through binding to angiotensin converting enzyme 2 (ACE2), and the responses of infected endothelial cell further accelerate the activation of two systems. For example, the decreased ACE2 increases the level of angiotensin II (Ang II) which leads to vasoconstriction and hyperinflammation. Infected endothelial cells release von Willebrand factor (VWF) and factor VIII that contribute to thrombus formation, and released angiopoietin 2 (Ang2) counteracts Ang1's anti-inflammatory actions through its receptor Tie2. Ang2 also increases vascular permeability that leads to the loss of anticoagulant proteins. Coagulation and inflammation are tightly connected, and interleukin (IL)-6 induce fibrinogen production, and thrombin binds to protease-activated receptor 1 (PAR1) which leads to proinflammatory reaction and platelet aggregation. Activated neutrophils also activate coagulation by releasing neutrophil extracellular traps (NETs) and damage-associated molecular patterns (DAMPs).

Figure 1