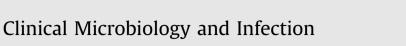Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Commentary

Thromboprophylaxis and anticoagulation for inpatients with COVID-19 in 2022 and beyond

Michael Dalager-Pedersen [1, 2, *]

[1] *Department of Infectious Diseases, Aalborg University Hospital, Aalborg 9000, Denmark*
[2] *Department of Clinical Medicine, Aalborg University, Aalborg 9000, Denmark*

In spring 2020, small observational studies suggested that COVID-19 was associated with a high risk for thromboembolic events, mainly within the venous compartment (VTE) as pulmonary embolism (PE) and deep venous thrombosis in patients managed in intensive care units (ICU). Despite lack of data from randomized clinical trials, guidelines on thromboprophylaxis and anticoagulation (AC) rapidly emerged with recommendations on thromboprophylaxis for most patients hospitalized with COVID-19 and intermediate or therapeutic dose AC for ICU patients, endorsed by international societies.

Today, two years later, thromboprophylaxis and AC for COVID-19 is guided by data from laboratory experiments, observational cohort and case-control studies, and randomized clinical trials. Laboratory data show that COVID-19 induces bidirectional interaction between the inflammation and coagulation systems causing a hypercoagulable state, which may lead to large-vessel macro

thrombosis, and endotheliopathy, which may confer small-vessel *in situ* immunothrombosis. Observational studies and clinical trials still find that COVID-19 is associated with thromboembolism, but in contrast to original reports, more recent risk-estimates clearly point to a much lower risk for VTE in COVID-19 with earlier SARS coronavirus 2 (SARS-CoV-2) variants (PE in approximately 4% and deep venous thrombosis in approximately 0.5%) [1,2]. In addition, thrombi are often located peripherally in the lung where diagnosis is challenging, overdiagnosis may occur, and clinical relevance is more unclear [3–6]. Randomized clinical trials have examined the effect of thromboprophylaxis and AC for COVID-19 among outpatients and among inpatients with differing disease severity. Placebo-controlled trials among outpatients at high risk for severe COVID-19 have not found AC to protect against disease progression or VTE [7]. Among ICU patients, therapeutic AC has failed to improve outcomes compared to usual-care thromboprophylaxis [8]. Among the inbetweeners, hospitalized noncritically ill patients with COVID-19, randomized trials offer inconsistent findings on the effect of therapeutic AC vs. usual-care thromboprophylaxis. In this patient group, the largest trial of 2219 patients detailed statistically nonsignificant differences in thrombotic events and bleeding, number needed to treat (NNT) for benefit of 100 (major thrombotic event in 1.1% vs. 2.1%) and a NNT for harm of 100 (major bleeding in 1.9% vs. 0.9%) [9]. Importantly, there was no effect on mortality. A recently updated meta-analysis on prophylactic AC trials in noncritically ill patients with COVID-19 found that dose escalation was not associated with a reduction in all-cause death but with an increase in major bleeding and a reduction in VTE [10]. Since update of the meta-analysis, the Swiss COVID-HEP trial has been published, the Standard vs High PROphylactic doses of anticoagulation in patients with high risk of THROMbosis admitted with COVID-19 pneumonia (PROTHROMCOVID) trial is in pre-print yet to be peer-reviewed, the Australasian COVID-19 trial (ASCOT) has closed the anticoagulation domain, and all three trials indicate a lack of benefit from higher dose AC [11–13].

Published trials on therapeutic AC vs. usual-care thromboprophylaxis in COVID-19 share some notable defining traits. Firstly, trial populations have been highly selected and at worst only 2.2% of screened patients have been randomized with underrepresentation of several vulnerable patient populations, e.g., those with

cancer, impaired liver and kidney function, conferring substantial negative impact on trial generalizability [14]. Secondly, no trial on hospitalized patients has included a placebo group. Thirdly, trials have been open label with introduction of ascertainment bias in regard to VTE events (i.e., a lower threshold for VTE diagnostic examination among patients on usual-care thromboprophylaxis) and major bleeding events (i.e., closer monitoring for bleeding in patients receiving higher doses of anticoagulants). As COVID-19 pneumonia clinically mimics PE, the risk for ascertainment bias may be high even though some trials employed an independent blinded clinical event committee to adjudicate outcomes. Finally, to rapidly attain sufficient statistical power and provide trial evidence, composite outcomes have been the norm, and none of the open-label trials selected mortality as the primary study outcome, although all-cause mortality is of paramount concern and free from ascertainment bias.

In their cohort study, Lund et al. address some of the traits shared by trials on thromboprophylaxis in COVID-19 [15]. The authors used healthcare records from Capital Region, Denmark, and Karolinska University Hospital, Sweden, to include all individuals admitted to hospital with a relevant positive reverse transcriptase polymerase chain reaction test and initial management outside of the ICU. To provide an estimate of the causal effect of "low dose" thromboprophylaxis vs. no thromboprophylaxis on 30-day mortality, VTE, and bleeding, they used inverse probability weighting for confounder adjustment and binomial regression for risk ratios and risk differences. The study included 1938 COVID-19 patients who received thromboprophylaxis within 48 hours of admission, and 1622 who did not. Overall, thromboprophylaxis was not associated with a lower mortality (risk ratio (RR), 0.89; 95% CI, 0.61—1.29) or bleeding risk (RR, 0.60; 95% CI, 0.14—2.59). Very few patients received a diagnosis of venous thromboembolism, especially in Denmark. Thus, only Swedish data allowed for comparison of VTE diagnosis, again with a statistical and clinical nonsignificant difference (RR, 0.68; 95% CI, 0.33—1.38, and risk difference -1.3%, 95% CI, -3.8% to 1.3%).

An obvious limitation to the study by Lund et al. is its non-randomized nature and potentially residual confounding. Moreover, ascertainment bias regarding VTE and bleeding is also an issue in this cohort study as it is in the open-label randomized trials. Still, the study by Lund et al. supports results from a recent Cochrane review that found an uncertain effect of anticoagulants in any dose on COVID-19 related mortality, VTE, and major bleeding [16]. It also supports the conclusion from the Cochrane review on a need for trials that include an arm with no anticoagulation in patients hospitalized with COVID-19 as no such trial exists.

To move forward, we should first look back. Before COVID-19, many infectious diseases were found to be associated with interaction between inflammation and coagulation, a hypercoagulable state, endotheliopathy, and an increased risk for thromboembolic events. Moreover, low-molecular weight heparin once garnered a lot of attention as being pivotal in thromboprophylaxis for hospitalized medical patients. However, a large meta-analysis and later the LIFENOX trial found no effect on usual-care thromboprophylaxis vs. placebo on mortality in hospitalized medical patients including those with severe systemic infection [17,18].

The study by Lund et al. and previous lessons on scant beneficial effect from thromboprophylaxis with heparin should help ignite interest in further studies on thromboprophylaxis and AC in COVID-19. Recent developments suggest mitigated interaction between the inflammation and coagulation systems in COVID-19 that should add further fuel to the flame. Growing population immunity from natural infection and vaccines may have altered the inflammatory response in COVID-19 and the accompanying hypercoagulability

and immunothrombosis [19]. New and emerging SARS-CoV-2 variants that cause less severe disease with little peri-bronchial and pulmonary inflammation may also lessen *in situ* immunothrombosis and risk for VTE in COVID-19 [20,21]. Immunomodulatory agents that affect coagulopathy are increasingly used to treat hyperinflammatory COVID-19 and are associated with lower mortality [22,23].

For many reasons, we need up-to-date population-based observational studies with data on circulating variants to better define who may, and who may not, benefit from AC during hospitalization with COVID-19. We also need additional large and more inclusive trials on the effect of giving no, low, or higher dose AC on mortality in COVID-19, especially after the arrival of the Omicron variant.

An impressive, concerted effort by medical and research communities helped us to better understand and manage COVID-19 under enormous pressure in early 2020. Now, the struggle continues to develop rigorous scientific evidence with the highest standards to improve treatment in an ever-changing COVID-19 in 2022 and beyond.

Transparency declaration

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