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.

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Editorial

Interpreting recent clinical studies for COVID-19: A continual process with more new data

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For clinicians, an early lesson learned from Coronavirus disease 2019 (COVID-19) was the hypercoagulability and risk of venous thromboembolic (VTE) complications associated with the SARS-CoV-2 viral infection. In 2020, a meta-analysis of 66 studies reported a total VTE incidence of 14.1%, but 22.7% in critically ill intensive care unit (ICU) patients [1]. Other studies also reported elevated D-dimer levels, likely reflecting clot burden, correlated with survival [2]. An increasing number of clinical trials evaluating optimal anticoagulation management strategies continue to be reported, with more not yet completed. Most studies evaluate low molecular weight heparin (LMWH) and unfractionated heparin (UFH) in escalated doses considered intermediate intensity or therapeutic intensity compared with standard prophylactic dose, with different dose strategies also based on illness severity, specifically ward *versus* ICU patients, while outpatient studies focus primarily on oral anticoagulants.

In this journal, Godon, from several French societies, propose updates to their previous 2020 report on therapeutic approaches to prevent VTE in patients with COVID-19 to reflect recently published information [3]. The authors suggest standard-dose prophylactic anticoagulation for inpatients and selected high-risk outpatients; intermediate or therapeutic-dose prophylactic anticoagulation in critically ill patients depending on the D-dimer level based on hospitalization duration, transitioning from an escalated dose started at admission to standard prophylactic dose 7–10 days after admission to reduce bleeding risk. For therapeutic-dose prophylactic anticoagulation patients, they suggest routine screening for thrombosis before dose alterations, weight-adjusted dosing, and haemostatic monitoring when using higher doses of heparin (anti-Xa activity).

How do we interpret these recommendations with the growing numbers of clinical trials of different antithrombotic strategies for COVID-19 [4–8]? The recent HEP-COVID randomized clinical trial (RCT) evaluating whether therapeutic dose LMWH thromboprophylaxis reduced thromboembolism and death compared with prophylactic/intermediate-dosing from high-risk COVID-19 patients was recently reported and not included in this guidance statement [4]. In 253 patients evaluated over a year, the composite of death or major thromboembolism was 28.7% with therapeutic-dose anticoagulation *vs.* 41.9% with prophylactic/intermediate-dose heparins, but only in non-critically ill patients. Inclusion criteria were D-dimer levels over 4 times the upper limit of normal (ULN) or sepsis-induced coagulopathy (SIC) score of 4 or more. Major bleeding was 1.6% with standard-dose *vs.* 4.7% with therapeutic-dose heparins. In the HEP-COVID trial, the primary endpoint, a composite of thrombotic events or death, does not include the need for organ support, a surrogate of progressive COVID-19. Of note, Moll et al. reported D-dimer levels in moderately ill *versus* ICU level of care and found the median peak D-dimer for moderately ill was 1050 ng/ml (ULN 500 ng/ml; range: 400−1400 ng/ml), so that these moderately ill patients would not have been included in HEP-COVID [8].

Other important recent studies include The Therapeutic Anticoagulation *versus* Standard Care as a Rapid Response to the COVID-19 Pandemic (RAPID) trial by Sholzberg et al., designed to determine if therapeutic heparin is superior to prophylactic heparin in moderately ill patients with D-dimer levels 2 times ULN on hospital ward admission [5]. In moderately ill patients, therapeutic heparin did not reduce the primary outcome of progression to mechanical ventilation, ECMO, or death, but decreased 28-day mortality with a low risk of major bleeding. However, many clinicians viewed the RAPID trial as negative because the primary outcome events were low, the 28-day mortality signal was small, and the study was underpowered.

More recently, the parallel Therapeutic Anticoagulation with Heparin in Critically Ill Patients with COVID-19 adaptive, multiplatform, RCT (n = 1098) evaluated critically ill patients receiving therapeutic or thromboprophylaxis doses with standard management [6]. The primary outcome was organ support–free days without cardiopulmonary support to day 21 and surviving to hospital discharge. The study was stopped due to futility, as survival to hospital discharge was 62.7% *vs.* 64.5%, with no difference in organ support free-days.

The other parallel RCT evaluated hospitalized non-critically ill COVID-19 patients, defined as an absence of critical care level organ support on enrollment [7]. Patients were randomized to receive either therapeutic-dose or usual-care pharmacologic

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thromboprophylaxis with heparins. The primary outcome was organ support-free days: days free of cardiovascular or respiratory organ support to day 21 among patients who survived to hospital discharge. The trial was also stopped after 2219 patients due to failure to meet prespecified criteria for the superiority of therapeutic-dose anticoagulation. However, the adjusted absolute between-group difference in survival until hospital discharge without organ support in the therapeutic-dose anticoagulation was only 4.0%, with major bleeding in 1.9% in therapeutic dose compared to 0.9% in the thromboprophylaxis groups.

Using HEP-COVID criteria to select for therapeutic dose anticoagulation qualifies as "carefully consider" as in the statement: *Based on these still evolving data we advise that moderately ill patients be carefully considered for therapeutic dose anticoagulation with a determination of individual net clinical benefit in the absence of objectively confirmed VTE.* (ASH FAQs: https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation, accessed 11/30/21) With the increasing number of vaccinated patients, and better patient management strategies, perhaps the number of critically ill patients has decreased, although hospital admissions for COVID-19 continue to climb currently, primarily in unvaccinated patients.

How do we interpret this evolution of clinical management strategies based on recent randomized studies? There is growing data that therapeutic anticoagulation dosing has a signal for decreased VTE (macrovascular thrombosis) in hospitalized patients who have advanced to a critically ill state. It is the question of "turning the tide" of COVID-19, that is, whether higher levels of anticoagulation can prevent microvascular thrombotic progression and multiorgan injury.

Adding complexity to interpreting the data is defining critical illness, a term that we understand intuitively but is more difficult to define. In general, we believe critical illness represents a requirement for at least one organ support (*e.g.*, oxygen for acute lung injury or vasoconstrictor and/or inotropic agents for shock), and the consideration the patient is at an increased risk for deterioration requiring additional support. Although most assume that ICU patients are critically ill, ICU admission criteria vary among institutions and are complicated by ICU bed availability in this era of COVID-19. In the multiplatform studies, the definition of non-severe hospitalised patient was an oxygen requirement of $\leq$ 6 l/min [7].

Further, in the multiplatform non-critically ill patient trial, the design and analysis leave additional questions regarding the significance of avoiding organ support if there is no difference in mortality; in this study, most patients survived to hospital discharge: 92.7%-therapeutic dose and 91.8%-standard of care (OR = 1.21 (0.87–1.68), an 87.1% superiority probability for therapeutic dose heparin. However, the difference between organ support-free days was only 4% at 21 days, and median value for organ support-free days 22 in both groups. For non-ICU ward patients, the therapeutic heparin arm appears to have a beneficial effect with Bayesian adjusted OR = 1.27 (95%; 1.03–1.58) [7].

These results are controversial for several reasons. First, participants assigned to each trial arm were recalculated based on a single interim analysis in 2020 to favor randomization to the therapeutic dose arm. This approach, called response-adaptive randomization, theoretically provides therapeutic advantages to study participants; however, it can also introduce selection bias, counteract initial randomization benefits, reduce total absolute numbers of individuals assigned to the favored arm, and lead to challenges interpreting the final results [9,10]. The chance for bias is greater when based on fewer or a single interim analysis, as was done in this trial. Second, it is challenging for a clinician to gauge whether an individual patient would have qualified for the trial. For example, participants who were thought to need hospitalization for 72 h or less were excluded, some sites only enrolled patients within 72 h of hospital admission, while others within 14 days of admission. Third, determining the benefits and risks of therapeutic dose prophylaxis for individual patients is challenging since major bleeding events were higher in the therapeutic dose arm. Although planned analyses to further assess outcomes/benefits are underway, guidelines vary widely.

For moderately ill COVID-19 patients, the difficulty determining which patients benefit from higher dose anticoagulation, the possibility of bias explaining the observed beneficial effects, and the elevated major bleeding risks make it challenging to recommend this strategy. Other factors should be considered, including potential differences between LMWH and UFH and concerns regarding heparin resistance in COVID-19 patients [11]. The current guidelines, as recommended by Godon, are important as they weigh individual VTE risk factors when deciding to start therapeutic dose heparin prophylaxis, similar to other studies reviewed. Unique to the proposal by Godon is the incorporation of hospitalization duration for COVID-19 to guide anticoagulation dosing. Although data supporting this anticoagulant approach are lacking, it makes intuitive sense that as the acute inflammatory response declines, so does the associated hypercoagulability but now with the potential for increased bleeding that includes added risks from prolonged ICU level care.

In summary, as we continue to gather more data about the role of anticoagulation in COVID-19 from additional RCTs in progress, guideline and guidance documents will likely continue to evolve. In addition, the critical role of vaccinations to prevent or attenuate this complex thromboinflammatory response of COVID-19 and the use of specific antiviral therapies that are rapidly evolving will further influence future recommendations.

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References

[1] Nopp S, Moik F, Jilma B, Pabinger I, Ay C. Risk of venous thromboembolism in patients with COVID-19: a systematic review and meta-analysis. Res Pract Thromb Haemost 2020;4(7):1178–91.
[2] Creel-Bulos C, Liu M, Auld SC, Gaddh M, Kempton CL, Sharifpour M, et al. Trends and diagnostic value of D-dimer levels in patients hospitalized with coronavirus disease 2019. Medicine (Baltimore) 2020;99(46):e23186. http://dx.doi.org/10.1097/MD.0000000000023186.
[3] Godon A, Tacquard CA, Mansour A, Garrigue D, Nguyen P, Lasne D, et al. Prevention of venous thromboembolism and haemostasis monitoring in patients with COVID-19: Updated proposals (April 2021): from the French working group on perioperative haemostasis (GIHP) and the French study group on thrombosis and haemostasis (GFHT), in collaboration with the French Society of Anaesthesia and Intensive Care (SFAR). Anaesth Crit Care Pain Med 2021;40(4):100919.
[4] Spyropoulos AC, Goldin M, Giannis D, Diab W, Wang J, Khanijo S, et al. Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19: the HEP-COVID randomized clinical trial. JAMA Intern Med 2021;181(12):1612–20.
[5] Sholzberg M, Tang GH, Rahhal H, AlHamzah M, Kreuziger LB, Ainle FN, et al. Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with covid-19 admitted to hospital: RAPID randomised clinical trial. BMJ 2021;375:n2400.
[6] Goligher EC, Bradbury CA, McVerry BJ, Lawler PR, Berger JS, Gong MN, et al. Therapeutic anticoagulation with heparin in critically ill patients with Covid-19. N Engl J Med 2021;385:777–89.
[7] Lawler PR, Goligher EC, Berger JS, Neal MD, McVerry BJ, Nicolau JC, et al. Therapeutic anticoagulation with heparin in noncritically ill patients with Covid-19. N Engl J Med 2021;385:790–802.

[8] Moll M, Zon RL, Sylvester KW, Chen EC, Cheng V, Connell NT, et al. VTE in ICU patients with COVID-19. Chest 2020;158:2130–5.
[9] Proschan M, Evans S. Resist the temptation of response-adaptive randomization. Clin Infect Dis 2020;71(11):3002–4.
[10] Park JJ, Thorlund K, Mills EJ. Critical concepts in adaptive clinical trials. Clin Epidemiol 2018;10:343–51.
[11] Levy JH, Connors JM. Heparin resistance — clinical perspectives and management strategies. N Engl J Med 2021;385(9):826–32.

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