Contents lists available at ScienceDirect

European Journal of Internal Medicine

A year later

Anticoagulant therapy for COVID-19: What we have learned and what are the unanswered questions?

1. Why is anticoagulation a therapeutic consideration in patient with COVID-19?

Venous thromboembolism (VTE), which comprises deep vein thrombosis (DVT) and pulmonary embolism (PE), and arterial thromboembolism (ATE), which includes myocardial infarction, ischemic stroke, systemic embolism, and peripheral arterial events, are common among hospitalized patients with coronavirus disease-2019 (COVID-19) and are major causes of morbidity and mortality. [1,2] The incidence of VTE in this population has been estimated between 5.5% to 14.1%, and such patients have a more than two-fold higher risk for developing VTE than matched controls [2,3]. This increased VTE risk has been attributed to microvascular thrombosis and systemic coagulopathy [4], while autopsy studies have identified unsuspected VTE or in situ pulmonary arterial thrombosis in more than 60% of patients with COVID-19 [5,6] Lastly, despite the administration of prophylactic-dose anticoagulation with a low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH), in accordance with initial (i.e., published in 2020) international guidance statements for hospitalized COVID-19 patients, such patients continued to develop VTE and ATE at high incidence rates (i.e., 20–30%), a phenomenon referred to as "breakthrough thrombosis". [7, 8]

2. What are the COVID-19 heparin trials and what are they investigating?

Given the apparent inadequacy of low-dose heparin to prevent thrombosis and other adverse outcomes in COVID-19, several randomized trials were launched to address the pivotal question of whether escalating the intensity of anticoagulation to therapeutic-dose (or full-dose) anticoagulant intensity could decrease the incidence of thrombosis and prevent overall clinical deterioration risk in hospitalized patients with COVID-19, without materially increasing their risk for major bleeding [7,9]. Globally, over 20 randomized trials (including the large multiplatform ATTACC, REMAP-CAP, and ACTIVE-IV trials) have

compared (within some trials ongoing) a strategy of therapeutic-dose anticoagulation compared with a prophylactic-dose (or low-dose) approach, in hospitalized COVID-19 patients. Most of these trials have distinguished patients according to disease severity, with separate analyses done in patients who are critically ill and require intensive care unit (ICU) level care and those with moderate-severity COVID-19 who require medical-ward level care. The primary outcomes assessed have varied across trials but most trials have included as primary or secondary outcomes VTE, ATE, all-cause mortality, survival without ventilation, ICU admission, organ support-free days, need for vasopressor treatment, and duration of hospitalization. [9] In a broader clinical context, these trials assess the use of anticoagulant therapy as an add-on treatment approach aimed at reducing the overall severity and morbidity related to COVID-19 pneumonia, while a minority have used a traditional anticoagulant trial design that focuses on reducing macrovascular thromboembolic events and related mortality.

3. What have we learned from the trials: when to use full-dose anticoagulants? when to avoid anticoagulants? UFH or LMWH? Effect of D-dimer status?

The past year has witnessed the emergence of several high-quality randomized trials in which, over time, there has been convergence of findings to support therapeutic-dose anticoagulation for hospitalized COVID-19 patients; however, this benefit appears limited to those patients with moderate disease severity and not requiring ICU level care. [10–13] First, the multiplatform trials (ATTACC, ACTIV-4a, and REMAP-CAP) demonstrated an increase in organ support-free days with therapeutic-dose LMWH or UFH in non-critically ill patients (adjusted odds ratio [OR] = 1.27; 95% confidence interval [CI]: 1.03–1.58), with an absolute treatment benefit more apparent in patients with high D-dimer (≥2 times the upper limit of the local laboratory normal [ULN]). [10] Secondly, the ACTION trial included hospitalized COVID-19 patients with elevated D-dimer (greater than the local laboratory ULN) and showed that therapeutic-dose rivaroxaban or enoxaparin followed by

rivaroxaban to day 30 did not improve clinical outcomes (time to death, duration of hospitalization, or duration of supplemental oxygen to day 30) (win ratio = 0.86; 95% CI: 0.59–1.22), while it increased major or clinically relevant non-major bleeding compared with prophylactic anticoagulation. [12] Thirdly, the INSPIRATION trial assessed ICU patients with COVID-19 and showed no difference between an intermediate-dose anticoagulant regimen (approximately 50% of therapeutic-dose) and a prophylactic-dose LMWH or UFH for the outcomes of VTE, ATE, need for extracorporeal membrane oxygenation (ECMO), or 30-day mortality. [13] Finally, the recently published HEP-COVID trial was the first randomized trial using a classic antithrombotic clinical trial design to show that in hospitalized COVID-19 patients with a D-dimer level ≥4 times the ULN, therapeutic-dose LMWH reduced a composite of VTE, ATE, and death, as compared with prophylactic-dose LMWH or UFH (relative risk [RR] =0.68; 95%CI: 0.49–0.96), without conferring an increased risk for major bleeding; this effect was observed in the non-ICU patients (RR = 0.46; 95% CI: 0.27–0.81) but not in ICU patients (RR = 0.92; 95% CI: 0.62–1.39). [14] Finally, the results of the RAPID trial in moderately-ill patients with elevated Dd did not show benefit of therapeutic heparin (mostly LMWH) versus prophylactic heparin to reduce the composite primary outcome of death, need for invasive/non-invasive mechanical ventilation, and admission to an ICU, but it significantly reduced the secondary outcome of death by 78% (0.22, 0.07 to 0.65; P = 0.006). [15] We await the publication of additional trials as well as prospective meta-analyses from the WHO and INVENT networks on the topic which should add clarity, but the totality of data showing benefit of therapeutic anticoagulation for moderate-severity COVID-19 pneumonitis in high risk subgroups with elevated Dd.

Based on these findings, a therapeutic-dose heparin regimen should be considered as a new treatment approach in non-ICU hospitalized patients with moderate-severity COVID-19 and an elevated D-dimer (Fig. 1). This strategy has potential to retard both microvascular thrombotic angiopathy leading to end-organ failure (as seen in the multiplatform trials) as well as its well-established effects in reducing classic macrovascular thromboembolic disease (as seen in the HEP-COVID trial). Although the recent update of the 2021 American Society of Hematology (ASH) Guidelines issued conditional recommendations in favor of prophylactic-intensity anticoagulation over intermediate-intensity or therapeutic-intensity anticoagulation for patients with COVID-19–related acute illness who do not have confirmed or suspected VTE, this is based on perceived inconsistencies of study designs, populations, intervention/comparators, outcomes, and analytic methods used across trials [16]. It is the opinion of this writing group that proper evaluation of results of the key randomized trials within a clinical context would lead to opposite conclusions, and antithrombotic guideline statements from other cardiovascular societies are forthcoming. More evidence is needed to assess whether therapeutic-dose heparins have potential to change the disease severity and thromboinflammation in hospitalized patients with COVID-19. The use of therapeutic-dose heparin in COVID-19 patients requiring ICU level care should be avoided given the lack of efficacy data and the potential for increased bleeding. Some of these findings are not unexpected as the anti-inflammatory effects of heparin are well-established; however, what is perhaps astonishing is that this is the first time in clinical practice where heparins, typically administered in doses use to treat acute thrombosis, have been used in patients without known thrombotic disease for its anticoagulant and pleiotropic non-anticoagulant effects. This paradigm shift may require time for widespread adoption into practice after adoption by guidelines, but clinicians can be reassured that administered therapeutic-dose heparin in moderate-severity COVID-19 appears safe, without a significant increase in the risk for
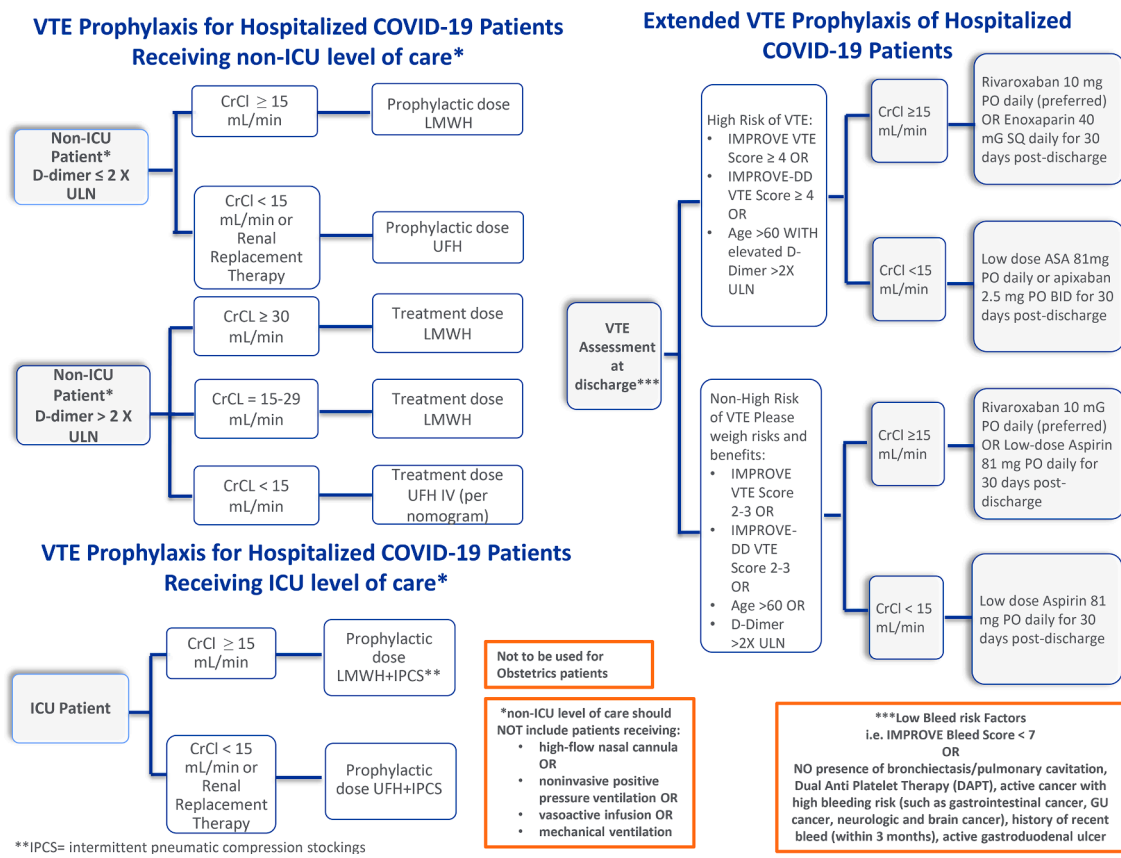

Fig. 1.. VTE Prophylaxis for Hospitalized COVID-19 Patients receiving non-ICU vs ICU level of care and extended VTE Prophylaxis in the post-discharge period (Adapted from Internal Northwell Health System Guidelines).

clinically important bleeding.

4. Unanswered questions: what if a moderately-ill hospital ward patient deteriorates and requires ICU care (or that an ICU patient transitions to non-ICU care)? What if a patient was receiving anticoagulant therapy prior to hospitalization? What happens to anticoagulant therapy after hospital discharge?

The optimal anticoagulant management in patients who progress from moderate to severe COVID-19 (or vice-versa) and in patients requiring ICU level care is uncertain. The benefit of therapeutic-dose heparins may indicate their multimodal effects (anticoagulant, anti-inflammatory, immunomodulatory, and antiviral) early in the course of COVID-19 to prevent both micro- and macrovascular thrombosis and the self-propagating positive feedback loop between coagulation and inflammation (thromboinflammation), before the development of an irreversible, overwhelming hyperinflammatory state and cytokine storm that may occur by the time a patient requires ICU level care [17]. Novel antithrombotic and other approaches in reducing the thrombotic burden in critically ill COVID-19 patients are needed, including the potential use of fibrinolytic agents, contact pathway activators, TF/VIIa complex inhibitors, and multimodal approaches.

The type of anticoagulant and the associated pleiotropic effects may be important and may explain why molecules potentially lacking these properties, such as direct oral anticoagulants (DOACs), are not equally effective. [12,17] There are currently no clinical data supporting the use of DOACs in COVID-19 inpatients. Based on the current evidence from the ACTION trial and the potential for multiple drug-drug interactions between DOACs and immunosuppressive/antiviral medications, hospitalized patients with moderate disease and previously on DOACs should be switched to treatment dose LMWH or UFH [18].

The optimal post-hospital thromboprophylaxis strategy, comprising the anticoagulant type, duration of treatment, and risks-benefit assessment is uncertain but is being actively investigated. The risk of VTE, ATE, and all-cause mortality remains high at up to 90-days after discharge and prophylactic-dose anticoagulants have been associated with a 46% decrease in the composite endpoint of major thromboembolism or all-cause mortality in a recent prospective registry of hospitalized COVID-19 patients [19]. The MICHELLE trial identified a high risk group of post-discharge COVID-19 patients using the IMPROVE VTE score ≥4 or elevated (≥2 times the ULN) D-dimer and found a 6% absolute risk reduction (67% relative risk reduction) for the composite primary outcome of major thromboembolism and cardiovascular death favoring rivaroxaban 10 mg daily for 30 days versus no anticoagulation (3.14% vs 9.43%, RR = 0.33; 95% CI: 0.13–0.90) [20]. Extended thromboprophylaxis with a DOAC may be considered for up to six weeks post-discharge in high-risk hospitalized COVID-19 patients (IMPROVE VTE score ≥4, increased D-dimer >2 times the ULN, >60 years and without bleeding risk factors, or recent ICU stay) (Figure 1) [21].

In summary, current data suggest the use of therapeutic-dose LMWH or UFH over standard heparin thromboprophylaxis to reduce VTE, ATE, organ support, and death among hospitalized patients with moderate COVID-19 and elevated D-dimer levels. In contrast, treatment dose heparins do not benefit, may increase bleeding, and should be avoided in hospitalized patients with severe COVID-19 in critical care settings. Hospitalized COVID-19 patients with high risk features (i.e., advanced age, IMPROVE VTE score ≥4, elevated D-dimer) should be considered for extended post-hospital discharge thromboprophylaxis with a DOAC. Lastly, randomized trials in this patient population are still ongoing and novel antithrombotic strategies in critically ill COVID-19 patients are needed.

Declaration of Competing Interest

The authors declare the following conflicts of interest:
DG: Broxmeyer Fellowship in Clinical Thrombosis

JDD: Janssen Consulting payment; Pfizer, BMS, Servier: Speaker/co-chair fee payments; Chair of 4 clinical trial of anticoagulant therapy for COVID-19

ACS: Research Grants – Boerhringer Ingelheim, Janssen, Agency for Healthcare Research and Quality; Research Grants – Boerhringer Ingelheim, Janssen, Agency for Healthcare Research and Quality

References

[1] Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in hospitalized patients with COVID-19 in a New York City health system. JAMA 2020;324:799–801. https://doi.org/10.1001/jama.2020.13372.

[2] 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. https://doi.org/10.1002/rth2.12439.

[3] Poissy J, Goutay J, Caplan M, Parmentier E, Duburcq T, Lassalle F, et al. Pulmonary embolism in patients with COVID-19: awareness of an increased prevalence. Circulation 2020;142:184–6. https://doi.org/10.1161/CIRCULATIONAHA.120.047430.

[4] Berger JS, Connors JM. Anticoagulation in COVID-19: reaction to the ACTION trial. Lancet Lond Engl 2021;397:2226–8. https://doi.org/10.1016/S0140-6736(21)01291-5.

[5] Lax SF, Skok K, Zechner P, Kessler HH, Kaufmann N, Koelblinger C, et al. Pulmonary arterial thrombosis in COVID-19 with fatal outcome: results from a prospective, single-center, clinicopathologic case series. Ann Intern Med 2020;173: 350–61. https://doi.org/10.7326/M20-2566.

[6] Wichmann D, Sperhake J-P, Lütgehetmann M, Steurer S, Edler C, Heinemann A, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. Ann Intern Med 2020;173:268–77. https://doi.org/10.7326/M20-2003.

[7] Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. J Am Coll Cardiol 2020;75:2950–73. https://doi.org/10.1016/j.jacc.2020.04.031.

[8] Spyropoulos AC, Levy JH, Ageno W, Connors JM, Hunt BJ, Iba T, et al. Scientific and standardization committee communication: clinical guidance on the diagnosis, prevention and treatment of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost JTH 2020;18:1859–65. https://doi.org/10.1111/jth.14929.

[9] Tritschler T, Mathieu M-E, Skeith L, Rodger M, Middeldorp S, Brighton T, et al. Anticoagulant interventions in hospitalized patients with COVID-19: a scoping review of randomized controlled trials and call for international collaboration. J Thromb Haemost JTH 2020;18:2958–67. https://doi.org/10.1111/jth.15094.

[10] ATTACC investigators. ACTIV-4a investigators, REMAP-CAP investigators. In: Lawler PR, Goligher EC, Berger JS, et al., editors. Therapeutic anticoagulation with heparin in noncritically ill patients with COVID-19. N Engl J Med; 2021. https://doi.org/10.1056/NEJMoa2105911.

[11] REMAP-CAP Investigators. ACTIV-4a investigators, ATTACC investigators. In: Goligher EC, Bradbury CA, McVerry BJ, et al., editors. Therapeutic anticoagulation with heparin in critically ill patients with COVID-19. N Engl J Med; 2021. https://doi.org/10.1056/NEJMoa2103417.

[12] Lopes RD, de Barros E, Silva PGM, Furtado RHM, Macedo AVS, Bronhara B, Damiani LP, et al. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. Lancet Lond Engl 2021;397:2253–63. https://doi.org/10.1016/S0140-6736(21)01203-4.

[13] Investigators INSPIRATION, Sadeghipour P, Talasaz AH, Rashidi F, Sharif-Kashani B, Beigmohammadi MT, et al. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: the INSPIRATION randomized clinical trial. JAMA 2021; 325:1620–30. https://doi.org/10.1001/jama.2021.4152.

[14] 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. https://doi.org/10.1001/jamainternmed.2021.6203.

[15] Sholzberg M, Tang GH, Rahhal H, AlHamzah M, Kreuziger LB, Áinle 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. https://doi.org/10.1136/bmj.n2400.

[16] Cuker A, Tseng EK, Nieuwlaat R, Angchaisuksiri P, Blair C, Dane K, et al. American Society of Hematology living guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19: may 2021 update on the use of intermediate-intensity anticoagulation in critically ill patients. Blood Adv 2021;5 (20):3951–9. https://doi.org/10.1182/bloodadvances.2021005493. Oct 26.

[17] Gozzo L, Viale P, Longo L, Vitale DC, Drago F. The potential role of heparin in patients with COVID-19: beyond the anticoagulant effect. A review. Front Pharmacol 2020;11:1307. https://doi.org/10.3389/fphar.2020.01307.

[18] Schutgens RE. DOAC in COVID-19: yes or no? HemaSphere 2020;5:e526. https://doi.org/10.1097/HS9.0000000000000526.

[19] Giannis D, Allen S, Tsang J, Flint S, Pinhasov T, Williams S, et al. Post-discharge thromboembolic outcomes and mortality of hospitalized COVID-19 patients: the CORE-19 registry. Blood 2021. https://doi.org/10.1182/blood.2020010529.

[20] Ramacciotti E, Agati LB, Calderado D, Aguiar VCR, Spyropoulos AC, de Oliveira CCC, et al. Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised controlled trial. Lancet 2021 (in press.

[21] Cohoon KP, Mahé G, Tafur AJ, Spyropoulos AC. Emergence of institutional antithrombotic protocols for coronavirus 2019. Res Pract Thromb Haemost 2020;4:510–7. https://doi.org/10.1002/rth2.12358.

Dimitrios Giannis[a,b], James D. Douketis[c], Alex C. Spyropoulos[a,b,d,*]

[a] *Institute of Health System Science, The Feinstein Institutes for Medical Research, Northwell Health, Manhasset, NY, USA*

[b] *Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York, USA*

[c] *Department of Medicine, McMaster University, Hamilton, Ontario, Abbreviation:*

[d] *Department of Obstetrics and Gynecology, I.M. Sechenov First Moscow State Medical University, Moscow, Russia*

[*] Corresponding author at: Professor of Medicine-The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Professor-The Institute of Health System Science, The Feinstein Institutes for Medical Research, System Director-Anticoagulation and Clinical Thrombosis Services; Northwell Health at Lenox Hill Hospital, 130 E 77th St, New York, NY 10075.

E-mail address: aspyropoul@northwell.edu (A.C. Spyropoulos).