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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Letter to the Editors-in-Chief

When to use anticoagulation in COVID-19☆,☆☆

Early in the COVID-19 pandemic, infection with SARS-CoV-2 was noted to be associated with a coagulopathy [1] and high rates of VTE observed in ICU patients, leading many to escalate doses of anticoagulants in infected ICU patients, as described by Kollias and colleagues. Many single and multi-institution analyses found increased VTE rates in ICU patients, based in part on how aggressively patients were assessed for VTE [2]. In the first 210 patients with COVID-19 admitted to our institution, we found a 3–4 fold increase in cumulative incidence of VTE in the ICU patients compared to those on the ward [3], resulting in a change in institutional practice to increased "intermediate" dose LMWH for thromboprophylaxis. Using propensity score matching, we found no difference in VTE or mortality with "intermediate dose" heparin anticoagulants, although with no concerning increase in major bleeding [4]. Review of past data on the effectiveness of standard dose VTE practice in ICU patients also factored into our decision making, as VTE rates were higher in this population than those on the ward [5].

Randomized controlled trials were launched to address appropriate dose of anticoagulants in hospitalized patients, both on the ward and in the ICU. Endpoints however were not just venous or arterial thrombosis but included organ failure and death, as data showing pulmonary microvascular thrombosis [6] suggested that death from hypoxemic respiratory failure was a result of COVID-19 associated coagulopathy. As Kollias and colleagues note and describe, we now have data from the published INSPIRATION trial comparing intermediate dose to standard dose heparin in ICU patients [7], and the multiplatform merged ATTACC/REMAP-CAP/ACTIV-4A (mpRCT) comparing therapeutic dose heparin to standard dose in both moderately- and severely-ill patients, although these data are not yet published in a peer reviewed journal. In both INSPIRATION and the multiplatform analysis in ICU patients, escalated dose of heparin did not result in a decrease in the outcome compared to standard dose. While Kollias suggests that "VTE represents the most relevant endpoint regarding anticoagulation" in the moderately ill patients in the ATTACC/REMPA-CAP/ACTIV-4A trial, use of therapeutic dose heparin conferred a survival benefit, with decrease in the composite outcome of organ support free days and death. With the staggering numbers of deaths across the globe from COVID-19, improved survival with anticoagulation is relevant.

Our findings that an increased dose of heparin did not affect rates of thrombosis or mortality in ICU patients are similar to the results of both INSPIRATION and the severely ill cohort of the mpRCT. Kollias, we, and others have suggested that the aggregate of these data indicate that the use of increased doses of heparins in severely ill patients may be too late to mitigate the thrombotic effects of COVID-19; starting earlier with higher doses of anticoagulants, as in the moderately-ill cohort of the mpRCT appears to be better. As pointed out by Kollias and colleagues, use of intermediate dose heparin in 95 patients admitted to the ward at their institution suggested improved outcomes [8], supporting the findings in the moderately-ill arm of the multiplatform trial.

RCTs have been designed to address the question of timing of when to start antithrombotics in COVID-19. A number of trials (NCT04498273, NCT00000614, NCT04400799) are enrolling acutely infected symptomatic patients that do not require hospital admission, including ACTIV-4b which randomizes to placebo, aspirin 81 mg a day, or prophylactic or treatment dose of apixaban (NCT04498273).

We eagerly await the results of these trials.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: M. Moll has no conflicts of interest. J.M. Connors reports personal fees for scientific Ad Boards and Consulting: Abbott, Anthos, Alnylam, Bristol-Myers Squibb, Portola, Takeda. Research funding to the institution from CSL Behring.

References

[1] J.M. Connors, J.H. Levy, COVID-19 and its implications for thrombosis and anticoagulation, Blood 135 (23) (Jun 4 2020) 2033–2040, https://doi.org/10.1182/blood.2020006000 (PMID: 32339221; PMCID: PMC7273827).

[2] S. Nopp, F. Moik, B. Jilma, I. Pabinger, C. Ay, Risk of venous thromboembolism in patients with COVID-19: a systematic review and meta-analysis, Res. Pract. Thromb. Haemost. 4 (7) (Sep 25 2020) 1178–1191, https://doi.org/10.1002/rth2.12439 (Epub ahead of print. PMID: 33043231; PMCID: PMC7537137).

[3] M. Moll, R.L. Zon, K.W. Sylvester, E.C. Chen, V. Cheng, N.T. Connell, L. E. Fredenburgh, R.M. Baron, M.H. Cho, A.E. Woolley, J.M. Connors, VTE in ICU patients with COVID-19, Chest 158 (5) (Nov 2020) 2130–2135, https://doi.org/10.1016/j.chest.2020.07.031 (Epub 2020 Jul 22. PMID: 32710891; PMCID: PMC7674987).

[4] M. Moll, R.L. Zon, K.W. Sylvester, J. Rimsans, E.C. Chen, A.J. Ghosh, E. Abston, A. Kim, H. Rutherford, X. Mitre, A. Hakim, N.T. Connell, E. Battinelli, L. E. Fredenburgh, R.M. Baron, B.D. Hobbs, M.H. Cho, M.A. Mittleman, A.E. Woolley, J.M. Connors, Intermediate versus standard dose heparin prophylaxis in COVID-19 ICU patients: a propensity score-matched analysis, Thromb. Res. 203 (Apr 19 2021) 57–60, https://doi.org/10.1016/j.thromres.2021.04.009 (Epub ahead of print. PMID: 33940309; PMCID: PMC8053596).

[5] W. Lim, M. Meade, F. Lauzier, R. Zarychanski, S. Mehta, F. Lamontagne, P. Dodek, L. McIntyre, R. Hall, D. Heels-Ansdell, R. Fowler, M. Pai, G. Guyatt, M.A. Crowther, T.E. Warkentin, P.J. Devereaux, S.D. Walter, J. Muscedere, M. Herridge, A. F. Turgeon, W. Geerts, S. Finfer, M. Jacka, O. Berwanger, M. Ostermann, I. Qushmaq, J.O. Friedrich, D.J. Cook, PROphylaxis for ThromboEmbolism in Critical Care Trial Investigators, Failure of anticoagulant thromboprophylaxis: risk factors in medical-surgical critically ill patients, Crit. Care Med. 43 (2) (Feb 2015) 401–410, https://doi.org/10.1097/CCM.0000000000000713 (PMID: 25474533).

[6] M. Ackermann, S.E. Verleden, M. Kuehnel, A. Haverich, T. Welte, F. Laenger, A. Vanstapel, C. Werlein, H. Stark, A. Tzankov, W.W. Li, V.W. Li, S.J. Mentzer, D. Jonigk, Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in

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Covid-19, N. Engl. J. Med. 383 (2) (Jul 9 2020) 120–128, https://doi.org/10.1056/NEJMoa2015432 (Epub 2020 May 21. PMID: 32437596; PMCID: PMC7412750).

[7] INSPIRATION Investigators, P. Sadeghipour, A.H. Talasaz, F. Rashidi, B. Sharif-Kashani, M.T. Beigmohammadi, M. Farrokhpour, S.H. Sezavar, P. Payandemehr, A. Dabbagh, K.G. Moghadam, S. Jamalkhani, H. Khalili, M. Yadollahzadeh, T. Riahi, P. Rezaeifar, O. Tahamtan, S. Matin, A. Abedini, S. Lookzadeh, H. Rahmani, E. Zoghi, K. Mohammadi, P. Sadeghipour, H. Abri, S. Tabrizi, S.M. Mousavian, S. Shahmirzaei, H. Bakhshandeh, A. Amin, F. Rafiee, E. Baghizadeh, B. Mohebbi, S. E. Parhizgar, R. Aliannejad, V. Eslami, A. Kashefizadeh, H. Kakavand, S.H. Hosseini, S. Shafaghi, S.F. Ghazi, A. Najafi, D. Jimenez, A. Gupta, M.V. Madhavan, S.S. Sethi, S.A. Parikh, M. Monreal, N. Hadavand, A. Hajighasemi, M. Maleki, S. Sadeghian, G. Piazza, A.J. Kirtane, B.W. Van Tassell, P.P. Dobesh, G.W. Stone, Lip GYH, H. M. Krumholz, S.Z. Goldhaber, B. Bikdeli, 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 325 (16) (Apr 27 2021) 1620–1630, https://doi.org/10.1001/jama.2021.4152 (PMID: 33734299; PMCID: PMC7974835).

[8] G. Poulakou, E. Dimakakos, A. Kollias, K.G. Kyriakoulis, V. Rapti, I. Trontzas, C. Thanos, M. Abdelrasoul, T. Vantana, K. Leontis, E. Kakalou, K. Argyraki, I. Baraboutis, E. Michelakis, E. Giamarellos-Bourboulis, K. Dimakou, G. Tsoukalas, A. Rapti, E.D. Michelakis, K.N. Syrigos, Beneficial effects of intermediate dosage of anticoagulation treatment on the prognosis of hospitalized COVID-19 patients: the ETHRA study, In Vivo 35 (1) (Jan–Feb 2021) 653–661, https://doi.org/10.21873/invivo.12305 (PMID: 33402523; PMCID: PMC7880792).

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