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Thromboprophylaxis strategies for COVID-19 patients

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Dear Editor,

We have read with interest the manuscript by Arigondam AK, et al. (1); the authors recommend that critical coronavirus disease (COVID-19) patients consider therapeutic anticoagulation strategies. We would like to share the following considerations and questions:

A preliminary interim analysis performed by the *Randomized, Embedded, Multifactorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP), Antithrombotic Therapies to Ameliorate Complications of COVID-19 (ATTACC),* and *Anti-thrombotics for Adults Hospitalized with COVID-19 (ACTIV-4a)* randomized trials recently reported the impact and implications of different thromboprophylaxis strategies in hospitalized patients with COVID-19, which showed that among critical COVID-19 patients that received therapeutic anticoagulation were most likely to have increased mortality (35.3% versus 32.6%), and furthermore, higher major bleeding events (1.8% versus 3.7%) (2,3). Should we be more cautious about using more aggressive fully therapeutic anticoagulation in the critical COVID-19 subgroup? The high predisposition of these patients to suffer a major episode of bleeding must be taken into consideration.

Arigondam AK, et al. have recommended the use of direct oral anticoagulants (DOACs) in the post-discharge period for 4–6 weeks (1). At this point we must make some considerations: the prothrombotic risk may persist up to 90 days post COVID-19 despite improvement of such severe acute pulmonary inflammatory insult, the patient's comorbidities and the degree of functionality and mobility of the patient at discharge. In other words, functional patients, with a high degree of mobility, without associated comorbidities or persistent hypercoagulable risk factors, may not require extended thromboprophylaxis with DOACs; on the other hand, patients with disabling neurological or cardiopulmonary diseases, prolonged immobilization, persistent risk factors like malignancy, chronic inflammatory diseases (e.g., inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus) and/or previous venous thromboembolism (VTE) may require extended thromboprophylaxis, proven they have low-risk for bleeding profile. Is there any prospective evidence-based data on the current use of DOACs as extended thromboprophylaxis strategies, particularly in patients with lengthy ICU and hospital stays? We personally believe that careful and cautious selection should be made while prescribing DOACs for extended thromboprophylaxis. Recently, IMPROVE-DD risk assessment model was prospectively validated as a valuable tool to aid on such complex decisions (4). We believe that detailed and careful screening and selection should be made while deciding to prescribe or not DOACs in post-discharged patients with COVID-19, rather than liberally recommend DOACs. Moreover, more robust prospective randomized data like the double-blind, placebo-controlled, pragmatic, event-driven phase-3 PREVENT-HD trial, which is currently evaluating the efficacy and safety of rivaroxaban in the outpatient setting to reduce thromboembolic events, hospitalization, and mortality associated with COVID-19 (5). Faced with a recent and little-known disease such as COVID-19, we must be cautious when prescribing and instituting thromboprophylaxis strategies, because there may be more risks than benefits in challenging case scenarios, despite a well-established correlation with thromboembolic events in COVID-19 patients, we believe that important scientific pieces of the puzzle are still lacking to draw solid conclusions on what are the best thromboprophylaxis strategies for best clinical practice in this emerging field of thrombosis. We propose an approach for thromboprophylaxis according to the severity of COVID-19 (6,7) (Table 1).

Finally, we would like to emphasize the potential impact and role of a dedicated, multidisciplinary, team-based approach, VTE response teams, which we believe they play an important part in the care and prevention of VTE in our hospitals; such multidisciplinary teams may individualize, and tailor the best thromboprophylaxis strategy for a given patient, for the best clinical decision making, prioritizing optimal patient care, outcomes, and survival for such devastating disease like VTE (8,9).

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Table 1. Thromboprophylaxis strategies in patients with COVID-19 according to the degree of severity

Severity classification (5)	Thromboprophylaxis strategy	Considerations
Critical coronavirus disease (COVID-19)		
Acute respiratory failure, septic shock, and/or multiple organ dysfunction/failure	Thromboprophylaxis with standard doses of LMWH or UFH (individualize thromboprophylaxis strategies according to unique patients' characteristics)	Constantly monitor clinical signs and symptoms of thrombosis and bleeding
Severe COVID-19		
Dyspnea, respiratory frequency ≥30/min, blood oxygen saturation≤93%, PaO_2/FiO_2 ratio <300, and/or lung infiltrates >50% within 24–48 hours	Ongoing randomized clinical trials will dictate intensity and type of antithrombotic strategies (e.g. REMAP-CAP, ACTIV-4a, and ATTACC multiplatform trials)	
Mild COVID-19		
Non-pneumonia and mild pneumonia cases	No thromboprophylaxis for now. Undergoing studies are addressing which patients may be potential candidates for outpatient thromboprophylaxis while quarantining with elevated D-dimer (e.g., OVID trial)[6]	Patients without thrombotic risk

LMWH: low molecular weight heparin, UFH: unfractionated heparin, DOAC: Direct oral anticoagulants.

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