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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Clinical Insights

Anticoagulation as secondary prevention of massive lung thromboses in hospitalized patients with COVID-19

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Since February 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been responsible for one of the major pandemic we have experienced in the last 100 years [1]. The most severe clinical presentation of COVID-19 is through acute respiratory distress syndrome (ARDS) classifying it as a respiratory illness. The presence of an underlying hypercoagulable state, associated to venous thrombotic events with a prevalence of 30%, was extensively reported worldwide in COVID-19 patients [2–4]. Moreover, several autopsy studies reported microvascular thromboses in lungs and most organs of deceased patients [5,6].

SARS-CoV-2 infection is thought to be responsible for a specific mechanism of thrombo-inflammation, called the "immunothrombosis model" [7]. The viral-mediated direct cellular damage and the immune response result in the release of proinflammatory cytokines. Cytokines determine the subsequent activation and dysfunction of the endothelium, which contributes to the establishment of an immuno-mediated hypercoagulable state [8]. The pro-thrombotic state is a condition that may precede morbidity and mortality.

According to Ciceri et al. [9], this atypical ARDS working hypothesis was named microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS). This syndrome is thought to be caused by alveolar endothelial damage, followed by progressive endothelial pulmonary involvement. Subsequently, the inflammation and the thrombotic milieu also affect the microcirculation of other organs, eventually leading to multiple organ failure (MOF) [10] and, in certain circumstances, also to a disseminated intravascular coagulation-like state. Among COVID-19 patients with normal angiographic studies, thromboinflammatory markers (D-dimer, C-reactive protein, ferritin, and interleukin 6) are often elevated [11–13] suggesting the presence of microvascular damage. Nailfold videocapillaroscopy performed on COVID-19 patients showed microvascular abnormalities, resembling acute and post-acute microvascular damage [14]. Furthermore, the COVID-19 radiological pattern is characterized by a unique distribution of pulmonary venous thromboses (PVTs) which overlaps with lung inflamed areas, confirming that in situ thromboses are not embolisms [2].

Several international guidelines recommend heparin-based anticoagulation therapy in all COVID-19 hospitalized patients [15–20]. This recommendation is based on large observational studies [21,22] which support the efficacy of anticoagulation therapy, while randomized

Abbreviations: ARDS, acute respiratory distress syndrome; IL-6, interleukin-6 inhibitor; MicroCLOTS, microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome; MOF, multiple organ failure; PVTs, pulmonary venous thromboses; RCT, randomized clinical trials; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMA, thrombotic microangiopathy.

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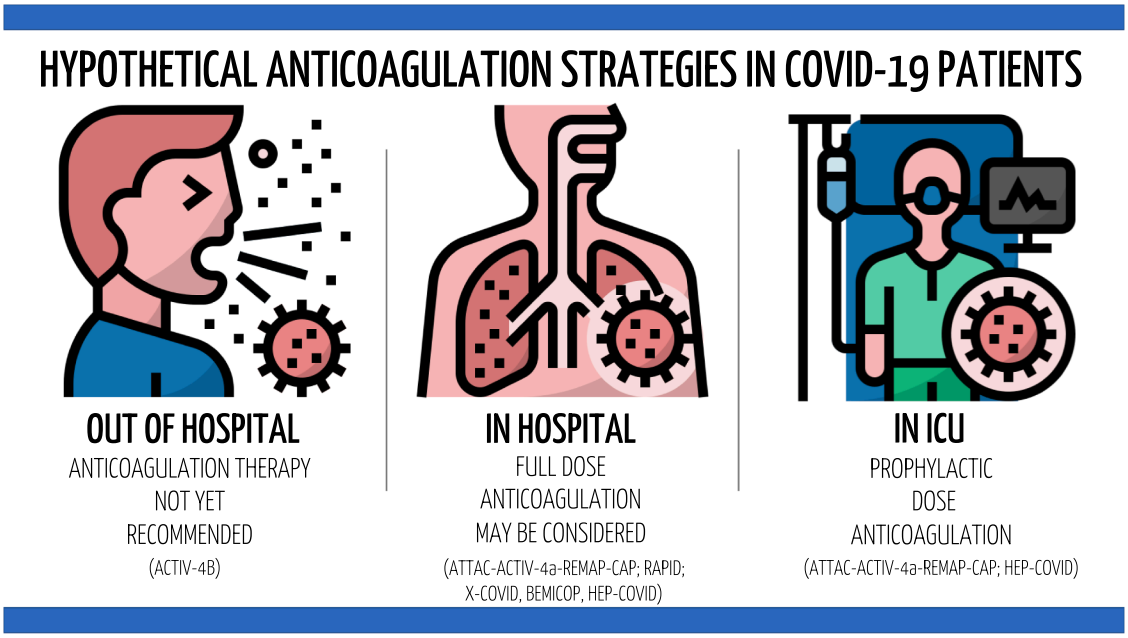

Fig. 1. Anticoagulation therapy in COVID-19 according to the disease severity.

clinical trials (RCTs) comparing the use of heparin versus placebo are lacking. Advantages of heparin include its antithrombotic, anti-inflammatory, and likely antiviral effects [23]. Moreover, heparin has fewer pharmacologic interactions with experimental drugs used in COVID-19 patients, alike the other oral anticoagulants. Despite all of these recommendations, the proper dosage of anticoagulant therapy (prophylactic vs full dose) and the exact time to start anticoagulants remain uncertain [24].

Large RCTs evaluated different anticoagulation strategies in critically ill (ATTAC-ACTIV-4a-REMAP-CAP, HEP-COVID) [25,26] and noncritically ill (ATTAC-ACTIV-4a-REMAP-CAP, RAPID, X-COVID, BEMICOP, HEP-COVID) [26–30] COVID-19 patients. According to these results, full dose anticoagulation (therapeutic dose) among non-critically ill patients may increase the probability of survival free of organ support, [27] the probability of 28-day survival, [28,30] and it may reduce the probability to developed venous thromboembolism (VTE) [29] with respect to prophylactic dose anticoagulation. However, these findings were not confirmed in patients treated in intensive care units (ICU) [25,26]. Although these RCTs did not include homogeneous populations and the mortality reduction was not confirmed in all studies, it is possible to hypothesize that the efficacy of the anticoagulation strategy may depend on the initiation time of the therapy with respect to the disease course.

If COVID-19 MicroCLOTS are similar to the immunothrombosis model, they are probably resistant to classical anticoagulants drugs. In this case, heparin may stop the progression of the coagulation cascade avoiding the increase in thrombi size, but is not able to dissolve clots. As a consequence, it may be reasonable to suggest that the rationale for the use of heparin would not be primary prevention, but secondary prevention and avoidance of thrombi progression and development of multisystemic thrombotic complications.

Within the context of mild-to-moderate respiratory illness, hospitalized SARS-CoV-2 infected patients may benefit from full-dose anticoagulation as secondary prevention. On the other hand, critically ill COVID-19 patients have probably already developed extensive lung thrombi. In this case, full-dose anticoagulation may not be able to reverse the established disease process. For these reasons, routine full-dose anticoagulation among ICU critically ill patients while not avoiding thrombotic complications can increase bleeding risk. Thus, anticoagulation therapy for critically ill COVID-19 patients should probably follow the same recommendation that are in place for critically ill non-COVID-19 patients.

Even if it reasonable to think that COVID-19 outpatients can benefit from (low dose) anticoagulants, a recent RCT showed no difference in clinical outcomes in patients treated with aspirin, apixaban, or placebo [31]. This might be attributed to the relatively low sample size of the study and/or to the use of drugs different from heparin. An observational large study also suggested that patients on chronic anticoagulants do not have reduced mortality if they develop COVID-19 [32].

As previously highlighted, Sars-CoV-2 exhibits a bidirectional crosstalk between inflammation and thrombosis, or immunothrombosis, and this unique mechanism of inducing coagulopathy paves the way to therapies including antithrombin supplementation, recombinant thrombomodulin, and multiple anti-inflammatory agents. Therefore, monoclonal antibodies targeting pro-inflammatory mediators have been proposed for the treatment of COVID-19 induced microvasculature injury and endothelial damage leading to thrombotic microangiopathy (TMA) [7,8]. Tocilizumab, an interleukin-6 inhibitor (IL-6), may reduce endothelial inflammation, microvascular thrombosis, and mortality [33–35].

Anakinra, an antagonist of interleukin 1 receptor, may dampen systemic inflammation, and reduce mortality [36] in COVID-19 patients, especially when administered early after hospitalization in moderate-to-severe patients outside the ICU. Future studies should investigate the concomitant use of therapeutic dose anticoagulation with anti-inflammatory drugs to prevent the development of critical illness and immunothrombosis.

Neutrophils extracellular traps (NETs) play a direct role in the immune-thrombotic process in COVID-19. Some experimental drugs, targeting NET formation, may limit endothelial damage and improve the prognosis [37]. Complement activation, secondary to endothelial injury, suggests the rational use of monoclonal antibodies against C5 and C3, such as Eculizumab and Ravulizumab (ClinicalTrials.gov Identifier: NCT04570397, NCT04288713, NCT04390464), for the treatment of COVID-19 associated thrombotic microangiopathy [38,39].

Summarizing all previous considerations, the hypercoagulable state associated with COVID-19 may be managed firstly by inhibiting the pro-inflammatory state and secondly by establishing anticoagulation at proper dosage, according to the disease course, to avoid the development or worsening of thrombotic complications.

In conclusion, our reasoning, which is supported by initial evidence, suggests that full anticoagulation maybe considered in non-ICU patients with COVID-19 at high risk of thrombosis progression and at low risk of bleeding. Other patients (eg ICU patients) might be routinely treated with prophylactic anticoagulants if not otherwise indicated. Further RCTs in homogeneous populations are needed to confirm these observations and to inform guidelines.

CRediT authorship contribution statement

RS: study conception and design, data interpretation, manuscript drafting. MC: data interpretation, manuscript drafting. GL: study conception and design, critical review of the manuscript. LD: study conception and design, manuscript drafting. AZ: study conception and design, critical review of the manuscript. All Authors read and approved the final version of the manuscript.

Declaration of Competing Interest

The authors report no conflicts of interest.

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