
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.

similar for the use of therapeutic heparin in patients with acute illness who are hospitalized with COVID-19. RCTs provide the best experimental design to study interventions; it is common to select participants who may gain the greatest benefit from the intervention. RCTs aim to provide evidence for relative treatment effectiveness under optimal conditions.[3] Such relative effects can often be applied to other populations, but physicians are required to estimate absolute risk differences that are based on relative benefits (or harms) and absolute baseline risks of an individual patient.[3]

Some of the alleged limitations of RCTs evaluating therapeutic dose heparin in patients with acute illness with COVID-19 need to be addressed.[1] First, the fact that 20% of participants who were allocated to the therapeutic heparin arm in the multiplatform trial received less than therapeutic dose anticoagulation is not a reasonable concern. If anything, nonadherence to the study protocol would have diluted treatment effects and biased effect measures towards the null. The same is true for inclusion of participants up to 14 days after admission in the REMAP-CAP trial. Of note, only 13% of the acutely ill patient population of the multiplatform trial was enrolled in REMAP-CAP. Second, although potential interaction by co-treatment is a potential concern, Jimenez et al[1] use this argument one-sided: What if therapeutic heparin diminishes the efficacy of other established treatments that were studied in patients who did not receive therapeutic heparin? The urgency to find effective treatments for a novel disease left investigators no choice but to study interventions simultaneously. Third, the assumptions that patients were kept on organ support because of the open-label trial design are unfounded, speculative, and unlikely, given the shortage of ICU beds during the pandemic. Furthermore, Jimenez et al[1] criticize that none of the trials included VTE in the primary outcome, except for the HEP-COVID trial. Ascertainment bias of thrombotic events was the exact reason that trials did not include VTE in the primary outcome or, when they did, performed screening ultrasonography as in the HEP-COVID trial. Finally, requiring supplemental oxygen was not part of the definition of organ support in the multiplatform trial. Furthermore, and as outlined in our editorial,[4] physicians can define the most relevant threshold of organ support-free days based on their individual preference because treatment effect measures of the multiplatform trial can be applied to any threshold of cumulative probabilities on the scale.

As for any treatment of COVID-19, uncertainties remain, given the rapid evolution of the pandemic, novel virus variants, and new preventive and therapeutic options. However, best current evidence from four RCTs support the use of therapeutic heparin in hospitalized patients with acute illness who are not at high risk of bleeding.

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# Rebuttal From Dr David Jimenez et al

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We thank our colleagues for their thoughtful insights in describing the potential role of therapeutic heparin in patients with COVID-19 who are not critically ill.[1]

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Therapeutic anticoagulation is not a minor intervention and is associated with harm,[2] mainly in the form of major bleeding. For this reason, for instance, there have been decades of research to establish the optimal duration of anticoagulation after an episode of VTE.[3] Therefore, we would like to take an opportunity to defend that therapeutic heparin use might not be generalized to all patients with COVID-19 who are not critically ill.

Our colleagues enthusiastically cite the literature that might support the role of empiric therapeutic anticoagulation in reducing the mortality rate in sepsis outside the COVID-19 setting.[4] In the quoted meta-analysis, the risk ratio for death comparing heparin with placebo or usual care was 0.88 (95% CI, 0.77 to 1.00). After exclusion of the three placebo-controlled trials, the mortality rate was not reduced significantly with the use of heparin (risk ratio, 0.67; 95% CI, 0.34 to 1.30). To our knowledge, none of the existing guidelines or clinical practice statements recommend (or even suggest) the use of therapeutic heparin in this scenario.[5] Specifically for patients with COVID-19 with critical illness, multiplatform randomly controlled trials (mpRCT) that were evaluating the role of therapeutic heparin were stopped because of futility.[6]

Many colleagues, including Tritschler et al, invoke both the time window and the pleiotropic hypotheses to reconcile the apparently contradictory effects of therapeutic anticoagulation for hospitalized (critically ill and not critically ill) patients with COVID-19. According to the first hypothesis, the beneficial effect of therapeutic anticoagulation is diminished in patients with progressively more severe disease. If this were the case, the mpRCT for patients who were not critically ill might have shown a lower effect of therapeutic heparin in the lowest levels of the organ support free days scale. However, as correctly pointed out by our colleagues, this was not the case.[7] The pleiotropic hypothesis suggests that heparin has antiinflammatory and immunomodulatory properties beyond anticoagulation. Although these properties have been postulated many times for specific subgroups of patients who did not have COVID (eg, cancer patients), studies have never been able to demonstrate a clinical benefit so far. According to the prinicipe of parsimony, our interpretation of the results of randomized trials that assess the efficacy and safety of therapeutic anticoagulation for patients both with and without critical illness who are hospitalized with COVID-19 is simple: significant reduction in VTE, significant increase in major bleeding, and no significant reduction in mortality rate.[2] Only in the mpRCT therapeutic heparin showed a significant reduction in the proportion of patients without requirement of organ support. However, (1) it had an open-label design, (2) participants assigned to each trial arm were recalculated based on a single interim analysis in 2020 to favor randomization to the therapeutic dose arm,[8] (3) roughly 40% of the patients who were enrolled the trial were not receiving standard of care treatment (ie, steroids) for COVID-19, (4) there was no significant difference in mortality rates, and (5) since the median value for OSFD was identical in both groups, the study had to report the proportion of patients in each treatment group who survived until hospital discharge without receipt of organ support.

In the recent times, there has been increasing vaccine coverage (with massive reductions in serious disease among populations with high vaccination rates), and the standard of care for patients with COVID-19 has evolved (including, but not limited to, monoclonal antibodies, dexamethasone, or tocilizumab). Also, the newest variants like omicron have milder forms of clinical presentation. Taken all together, we wonder whether the thrombogenic potential of SARS-CoV2 might have decreased.[9] This may tilt the balance of risk vs benefit of therapeutic anticoagulation in coming times.

At this point, International Society of Thrombosis and Haemostasis, CHEST, and the National Institutes of Health suggest the use of therapeutic heparin for patients who are not critically ill, who are hospitalized with COVID-19 and who have low bleeding risk (Table 1).[10] If such a treatment is chosen outside of a trial, shared decision-making should be made with patients about potential benefits, as well as existing uncertainties of this choice. We also would like readers to be aware that an American College of Clinical Pharmacy expert panel report on COVID-19 anticoagulation is subject for periodic update

**TABLE 1** ] High Bleeding Risk[9]

| |
|---|
| Bleeding within last 30 days that requires acute care setting |
| History of inherited or acquired bleeding disorder |
| Hemoglobin $< 8$ g/dL |
| Platelet count $< 50 \times 10^9$/L |
| Dual antiplatelet agents |

Bleeding risk should be individualized and discussed on a case-by-case basis.

because more evidence may emerge in coming times on this very critical issue (ie, FFREEDOM trial [NCT04512079]).

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