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Updated meta-analysis of randomized controlled trials on the safety and efficacy of different prophylactic anticoagulation dosing regimens in non-critically ill hospitalized patients with COVID-19

We thank Prof. Čulić and colleagues for their interest in our meta-analysis on the safety and efficacy of different prophylactic anticoagulation dosing regimens in coronavirus disease 2019 (COVID-19) patients.[1] Throughout the COVID-19 pandemic, the high rate of thromboembolic events among COVID-19 patients has been a topic of extensive and ongoing research.[2,3] Several randomized controlled trials (RCTs) have tested different anticoagulation regimens for preventing thromboembolic events.[1] However, the results of the RCTs have not been univocal, and the majority of these lack statistical power for individual hard endpoints such as death. For these reasons, we pooled the data on the safety and efficacy of prophylactic anticoagulation at escalated dose vs. standard dose in critically and non-critically ill hospitalized patients with COVID-19. This meta-analysis did not find any mortality benefit of an escalated dose over the standard dose of prophylactic anticoagulation. Moreover, there was a reduction of venous thromboembolism (VTE) counterbalanced by increased major bleeding in patients treated with escalated-dose prophylactic anticoagulation compared with those treated with a standard dose.[1] As the evidence has constantly been evolving after the publication of our meta-analysis (14 September 2021), further RCTs have become available in the setting of non-critically ill hospitalized patients.[4–6] The HEP-COVID trial, published on 7 October 2021, is the most relevant.[4] We agree with the authors that in non-critically ill hospitalized patients, the data reported by the HEP-COVID and the ATTACC, ACTIV-4a, and REMAP-CAP trials may suggest improved outcomes with an escalated dose of prophylactic anticoagulation compared with the standard dose.[4,7] Briefly, HEP-COVID showed a reduction of the primary endpoint (composite of arterial or venous thromboembolic events and all-cause death) driven by a reduction of venous and arterial thromboembolism in the non-intensive care unit (ICU) stratum,[4] while the ATTACC, ACTIV-4a, and REMAP-CAP trials showed a reduction of organ support-free days, favouring escalated-dose prophylactic anticoagulation.[7] Thus, whether escalated-dose prophylactic anticoagulation compared with standard-dose could reduce an individual hard endpoint such as death remains to be proven. To address this issue, we updated our previous analysis focusing on non-critically ill hospitalized patients by including the three RCTs reported meanwhile. This updated version was performed using the same methodology of our previous report (PROSPERO registration CRD42021257203).[1]

Our updated analyses included a total of 3808 patients, 3306 patients from the previous report; 253 from HEP-COVID[4] using low-molecular-weight heparin or unfractionated heparin; 66 from the BEMICOP study[5] using bemiparin; and 183 from X-COVID[6] using enoxaparin. Among non-critically ill hospitalized patients, the incidence of all-cause death was 8.0% (157/1962) in the escalated-dose and 8.7% (160/1838) in the standard-dose prophylactic anticoagulation group. The incidence of major bleeding was 2.1% (41/1971) and 1.1% (20/1837) in the escalated-dose and standard-dose anticoagulation groups, respectively. Compared with standard-dose prophylactic anticoagulation, escalated-dose prophylactic anticoagulation was not associated with a reduction of all-cause death [relative risk (RR) 0.92, 95% confidence interval (CI) 0.58–1.46, $I^2 = 63\%$] but was associated with an increase in major bleeding (RR 1.92, 95% CI 1.13–3.28, $I^2 = 0\%$) (*Figure 1*). The number needed to treat (NNT) for all-cause death was 141, while the number needed to harm for major bleeding was 101. The incidence of VTE was 1.6% (29/1809) with the escalated-dose and 3.4% (57/1679) with the standard-dose prophylactic anticoagulation. An escalated-dose regimen was associated with lower rates of VTE events compared with the standard dose (RR 0.48, 95% CI 0.31–0.75, $I^2 = 0\%$) (*Figure 1*). The NNT for VTE was 56.

In conclusion, this updated version of our meta-analysis found results that were consistent with those previously reported. In non-critically ill hospitalized patients with COVID-19, compared with standard-dose prophylactic anticoagulation, the escalated dose was not associated with a reduction in all-cause death but with an increase in major bleeding and a reduction in VTE. Therefore, the risks may outweigh the benefits. Overall, the currently available evidence does not support indiscriminate use of escalated-dose prophylactic anticoagulation in non-critically ill hospitalized patients with COVID-19. However, the selective use of therapeutic-dose heparin for patients who have a D-dimer above the upper limit of normal, require low-flow oxygen, and have no increased bleeding risk may be an option according to the updated National Institute of Health recommendations.[8]

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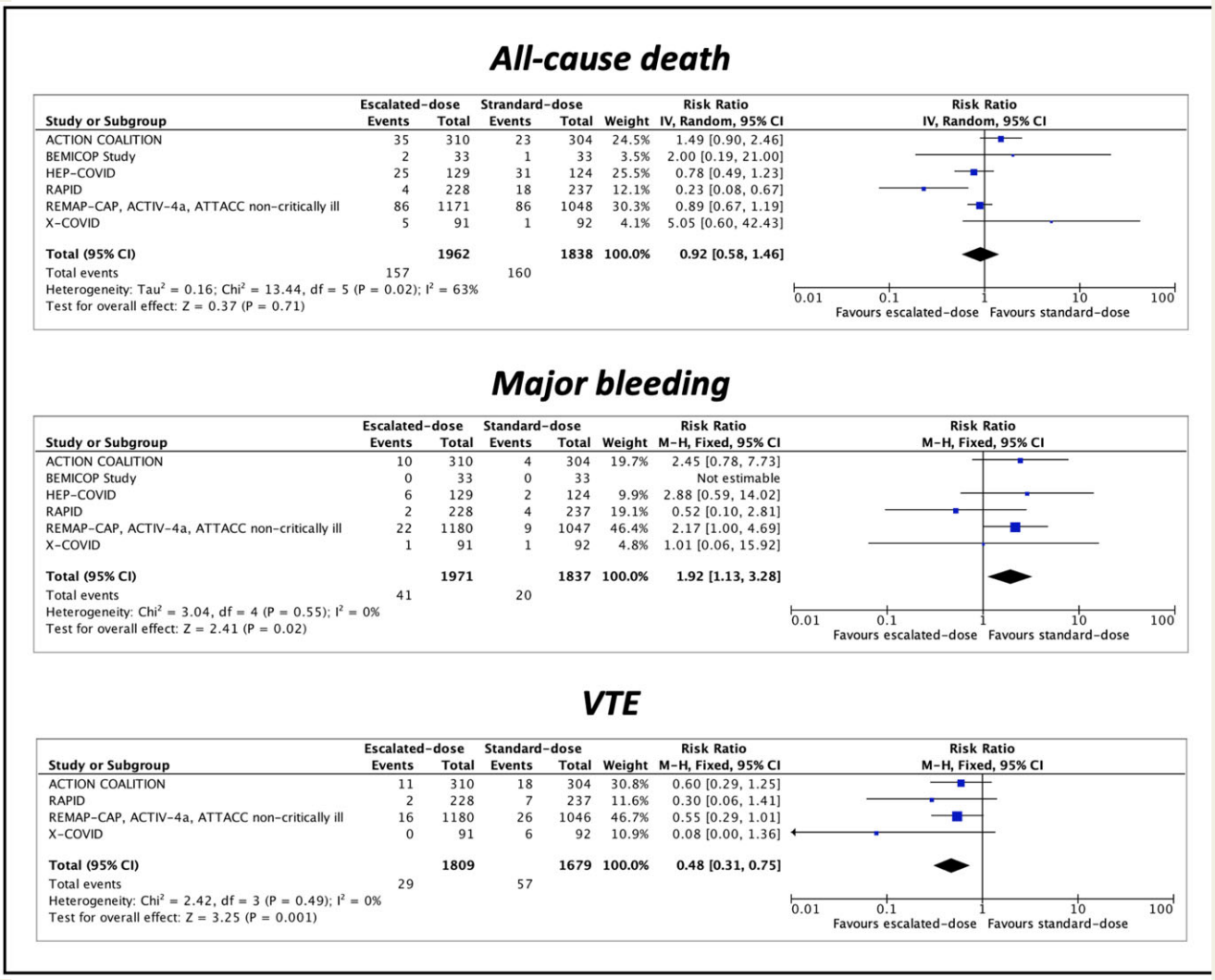

Figure 1 Forest plots of escalated-dose vs. standard-dose prophylactic anticoagulation in non-critically ill hospitalized patients with COVID-19 for all-cause death, major bleeding, and venous thromboembolism. CI, confidence interval; IV, inverse variance; M–H, Mantel–Haenszel; and VTE, venous thromboembolism.

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